BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

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BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON W.C.1

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BRITISH MEDICAL JOURNAL

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CHRONIC BRONCHITIS IN GREAT BRITAIN

A NATIONAL SURVEY CARRIED OUT BY THE RESPIRATORY DISEASES STUDY GROUP OF THE COLLEGE OF GENERAL PRACTITIONERS

Chronic bronchitis presents general practitioners with one of their most frequent and intractable problems. Since the decline in pulmonary tuberculosis it is now, with cancer of the lung, the most pressing in the field of respiratory disease. Although palliative treatment is possible and often rewarding, prevention should be the aim; and in a disease of such insidious onset general practitioners may have to carry the main burden. To advise and treat their patients with early bronchitis effectively they must have a more detailed knowledge of the nature and aetiology of the disease than any single experience can provide. With these needs in mind, the Research Committee of the College of General Practitioners formed in 1957, from its 600-strong "research register," a small group* to plan and execute a series of investigations into chronic bronchitis. This paper presents some preliminary findings of an epidemiological inquiry conducted within the framework of the National Health Service.

The excessive mortality from bronchitis in industrial areas and in poorer families is well known: and morbidity studies (Fairbairn and Reid, 1958; Logan and Cushion, 1958) have suggested a close relationship between air pollution and chronic bronchitis. Both these conclusions, however, derive from certificates of causes of disability or death usually given by general practitioners, so that the apparent social or geographical patterns may reflect differences between doctors in diagnostic habits and standards of certification. At the same time there have been suggestions that the effect of air pollution (Higgins and Cochran, 1958) and of cigarette smoking (Fry, 1954) on the prevalence of chronic bronchitis may be less than previous work had indicated. For these reasons the present survey was designed with four aims in mind:

1. To assess whether surveys by general practitioners using a standard clinical questionary can be used to find out the frequency of specified respiratory symptoms in a sample randomly selected from the population served by their practices.

2. To compare the prevalence of "chronic bronchitis" in various population groups as diagnosed by these general practitioners after completing the questionary (*a*) with the distribution of mortality and morbidity given by routine vital statistics and by other surveys; and (*b*) with the pattern based on a "standard diagnosis" derived from defined items in the questionary.

3. To gauge the value of a simple test of respiratory function (the Wright peak flow meter) (Wright and McKerrow, 1959) as a measure of disability in epidemiological studies in general practice.

4. To relate clinical assessments and the physiological test of respiratory disability to such variables as age, sex, smoking habits, and place of residence.

*Members of the Working Party: Drs. J. Fry (recorder), C. M. Fletcher, N. C. Oswald, D. D. Reid, C. H. Wood, H. W. K. Acheson, G. G. M. Edelsten, A. S. Fairbairn, J. C. Gilson, J. P. Horder, D. H. Lewis, R. F. L. Logan, W. J. H. Lord, J. Pemberton, P. A. Walford, and C. W. Ward.

Survey Methods

Questionary.—There is at present little agreement on the definition and diagnostic criteria of chronic bronchitis except that they are primarily based on symptoms (*Brit. med. J.*, 1959). In this study emphasis was placed on the prevalence of these respiratory symptoms; for this reason physical examination was omitted. A questionary on symptoms and on occupational, residential, and smoking histories was drawn up, and detailed instructions on its use were drafted. It was based on forms which had been used in several previous investigations (Higgins *et al.*, 1956, 1959; Fairbairn *et al.*, 1959).

Respiratory Function Test.—After questioning, the subjects were shown how to use the Wright peak flow meter. Five successive tests were made and the average of the last three results obtained was used in the analysis.

Sampling Procedure

Previous mortality and morbidity studies suggest that the age-group 45–64 is of crucial importance in the evolution of chronic respiratory disease. Samples were therefore drawn of men and women in each of the quinquennia 40–44, 45–49, 50–54, 55–59, and 60–64 from those on the practice lists of every doctor taking part in the survey. Although it was not possible to draw a representative sample from all British practitioners, the members of the College who agreed to take part were, as the list given below shows, working in rural and urban practices in areas scattered widely throughout the country. Through the helpful co-operation of the Ministry of Health and the executive councils and their staffs the record cards of all the patients on each doctor's practice list were sorted into age and sex groups. From each of the age and sex groups already defined, samples comprising one person from each group were taken in a random manner. At least three such samples were drawn from each practice list.

The doctors taking part were then asked to find and interview all the 10 members of the first of those samples. The importance of completing all the questionaries for these 10 patients rather than undertaking to do two such samples and examining only, say, 16 of the 20 patients selected was impressed upon them. If, however, a practitioner had completed his first sample, another sample was supplied on request. When local inquiry at the time of the survey showed that a selected patient had died or had moved from the district, a substitute, randomly selected from the appropriate

age and sex group was provided. By such independent control of the sampling process, bias in selection was avoided. Further, the structure of the sample ensured that each age and sex group was equally represented in the one or two samples seen by each doctor so that comparisons between doctors—for example, in different parts of the country—were based on samples balanced in this respect. On the other hand, the use of samples of a fixed size, and the latitude given to practitioners in examining one or two such samples, meant that the results could not give unbiased estimates of the frequency of the disease either in these practices or, even if practices had been randomly selected, in the country as a whole. In order to study the social factors in chronic respiratory disorder the practitioners were also asked to interview in the same way the wives of those men who were included in the random sample.

From the members of the College research panel 92 practitioners expressed a willingness to take part. Of the 1,630 individuals in the samples available for examination at the time of the survey, 1,569 (787 men and 782 women), or 94%, were seen; and the wives of 442 men thus selected were also interviewed.

Summary of Results

Although the 92 doctors taking part in the survey cannot be taken as representative of all general practitioners in the British National Health Service, the individuals surveyed, except for the wives of the men in the sample, were randomly selected from the practice lists and thus are typical of the populations in each age and sex group. In Table I the proportions of persons reported as married, single, widowed, or divorced found in the sample are compared with the proportions expected in a sample of that age and sex structure at the national rates recorded in the 1951 Census. Both in Table I and in Table II, which shows similar results in respect of social class, there is reasonably close agreement between the distributions. Again, Table III shows a remarkable consistency in the smoking habits in different groups of the sample and those of a sample surveyed in 1958 in a survey reported by Todd (1959). For many practical purposes, then, this sample may give a useful picture of the national experience of respiratory disability and its associated factors. The distribution of

TABLE I.—*Distribution by Marital Status in Sample Compared With Expectation at National Age–Sex Specific Rates (England and Wales 1951 Census). (Ages 40–64)*

	Married		Single		Widowed or Divorced		Marital Status Unknown	
	G.P.	E.W.	G.P.	E.W.	G.P.	E.W.	G.P.	E.W.
Males (%) ..	88	86	7	9	4	5	2	—
Females (%) ..	76	71	10	15	11	14	2	—

In Tables I–III G.P. = General practitioner survey population, and E.W. = Census population of England and Wales.

TABLE II.—*Social Class Distributions Based on G.P. Survey and 1951 Census Results (Ages 40–64)*

	Social Class									
	I		II		III		IV		V	
	G.P.	E.W.	G.P.	E.W.	G.P.	E.W.	G.P.	E.W.	G.P.	E.W.
All males (%)	4	3	19	18	48	47	17	17	12	16
Wives (%) ..	5	4	19	18	49	47	18	16	10	15

TABLE III.—*Smoking Habits in G.P. Survey and Smoking Survey, 1958*

Present Smoking Habits	Males		Females	
	G.P.	1958 Survey*	G.P.	1958 Survey*
Cigarette smokers (%)	53	55	35	39
Pipe ,, ,,	9	8	—	—
Mixed ,, ,,	8	9	—	—
Total ,, ,,	75	72	35	39
Non-smokers (incl. ex-smokers) (%) ..	25	28	65	61

* Subjects over the age of 35 years.

place of practice and the frequency of bronchitis found for the 22 doctors completing only 10 or fewer questionaries differed little from those of the remaining 70 who attempted to complete 20, and the data from both groups have been put together.

In the absence of any agreed definition of bronchitis in symptomatic terms, the data were examined to identify those questions which were apparently used by practitioners to differentiate bronchitics from the remainder. Each practitioner was asked, on completing the interview, to note whether he thought that the patient suffered from chronic bronchitis, asthma, or any other chest disease. The records were then divided on this basis into "bronchitics" and "others," and the frequency of positive responses to each item on the questionary in each group was computed. Of the items thus reviewed, three (Table IV) stood out as both

TABLE IV.—*Questions Discriminating Between Bronchitics and Others*

Question	Males		Females	
	Bronchitics (137)	Others (650)	Bronchitics (63)	Others (719)
	Percentage Positive			
7. Do you bring up any phlegm at all on getting up or first thing in the morning in winter? ..	89	30	71	13
19. Do you get bouts of cough and phlegm lasting for at least three weeks each winter and for more than two winters?	73	12	75	8
24. Do you have to walk slower than people of your own age on the level because of breathlessness?	57	6	51	11

common enough in the two sexes and differing widely enough in frequency between the "bronchitics" and the "others" to be used as criteria for the discrimination of bronchitics which could be applied uniformly to all the patients included in the survey. As a means of ensuring some standardization in diagnosis three criteria were

TABLE V.—*Age–Sex Bronchitis Prevalence Rates*

	Age																			
	40–44			45–49			50–54			55–59			60–64			Total		
	No.	%B	%SD	No.	%B	%SD	No.	%B	%SD	No.	%B	%SD	No.	%B	%SD	No.	%B	%SD
Males	149	7	3	158	11	4	162	18	6	164	23	12	154	29	16	787	17	8
Females ..	162	6	3	152	7	2	163	5	2	157	12	6	148	12	5	782	8	3

In Tables V, VI, and VIII–XII No. = Number of subjects. %B = Percentage with "bronchitis" as diagnosed by practitioner. %SD = Percentage with standard diagnosis.

taken to define bronchitis—morning phlegm in winter, attacks of cough and phlegm lasting three weeks over the past two years, and breathlessness on the level. In the tables that follow, subjects with these three characteristics are grouped under the heading "standard diagnosis" (SD). The results thus obtained are compared in several tables with the distribution of the clinical diagnosis of bronchitis made by the general practitioners themselves.

Prevalence of Chronic Bronchitis by Age and Sex

Table V shows that in younger subjects chronic bronchitis was diagnosed almost as often in the women drawn in the sample as in the men. Thereafter there is a steady increase with age for men of approximately 1% per annum. The age gradient for women is much less steep, and, perhaps because of the smaller numbers, rather irregular. It amounts overall to an increase of about 0.3% per annum. The male:female ratio rises from 1.2:1 at age 40–44 to 2.4:1 at age 60–64. With the standard syndrome diagnosis the pattern is essentially the same.

The total male:female ratio for bronchitis as diagnosed by the practitioners is 2.13:1. This sex ratio is similar to that of 1.95:1 found at ages 45–64 for chronic bronchitis (502.1 in the International List) by Logan and Cushion (1958) but lower than the ratio of 3:1 found by Higgins and Cochran (1958) at the same ages in the Vale of Glamorgan. The sex ratios in the present survey, however, contrast sharply with those found in patients with bronchitis attending chest clinics (M.R.C., 1959), which rose from 1.75:1 at age 40–49 to 5.2:1 at age 60–69. They also differ greatly from the sex ratio of mortality recorded for bronchitis for the years 1951–5, which rose from 2.5:1 at ages 40–44 to 5:1 at ages 60–64 (Case and Harley, 1958).

Present Residence

For a preliminary comparison of the prevalence of chronic bronchitis in rural and urban areas the subjects were divided according to their present residences. These areas of present residence were classified on a scale of increasing urbanization from rural districts to county and metropolitan boroughs. The prevalence of chronic bronchitis as originally diagnosed by the practitioners in these areas is given in Table VI.

TABLE VI.—*Place of Residence and Bronchitis Prevalence Rates*

	Type of District									Total		
	Rural Districts			Urban Districts and Municipal Boroughs			County and Metropolitan Boroughs					
	No.	%B	%SD	No.	%B	%SD	No.	%B	%SD	No.	%B	%SD
Males	158	12	3	355	15	7	274	23	13	787	17	8
Females	170	8	2	332	7	2	280	9	6	782	8	3

It will be noticed that, while the prevalence of bronchitis as diagnosed by the practitioners in males is nearly twice as great in the county and metropolitan boroughs as in rural districts, there is no corresponding increase in women. These figures cannot be compared with the report of Logan and Cushion (1958), for in their report the rates for different areas are not given separately by sex and age; but for bronchitis at all ages and both sexes the prevalence in urban areas recorded in their study was 12.0 per thousand compared with 4.7 per thousand in rural areas. This gives a ratio of 2.5:1, which is similar to that found among men in our survey. The difference in bronchitis mortality between urban and rural areas is of about 2 to 1 in men and rather less in women (Registrar-General, 1954). On the other hand, when the "standard diagnoses" rates in this survey are compared, the rural:urban gradient in males becomes much steeper, and there is a suggestion of an increased prevalence among the females in the larger cities compared with the other areas. This finding would seem to imply that the rural practitioners were classifying as "bronchitic" those patients whose symptoms would not have been thought by city doctors severe enough to warrant that diagnosis. This difference in diagnostic threshold may reflect the prevalence of a milder form of the disease in country areas, and suggests that the rural:urban difference reported in official mortality and morbidity statistics may underestimate the true difference in disease incidence.

Smoking Habits

The pattern of tobacco consumption shown in Table VII is quite different in the two sexes. Only 7% of the men had never smoked regularly, and the proportion of non-smokers was higher in the younger than in the older men. Of the women, 56% were non-smokers; and the proportion rose from 44% at ages 40–44 to 69% at ages 60–64. While 12% of the men smoked more than 25 g. of tobacco a day (1 cigarette being taken as 1 g.) only 1% of the women smoked as much as this. Because of this difference in age and sex pattern of smoking it is difficult to make valid comparisons between the two sexes in the prevalence of bronchitis in relation to smoking, for there are two few non-smoking men and too few heavy-smoking women. Table VIII shows, however, that the prevalence of chronic bronchitis is very similar among men and women with comparable smoking habits except for a higher male prevalence among present smokers. Most women within this group certainly smoked fewer cigarettes than the average for the men. These findings are similar to those of Oswald and Medvei (1955), and suggest that the difference in prevalence of chronic bronchitis in the two sexes may be largely accounted for by differences in smoking habits. The relatively high prevalence of bronchitis among ex-smokers (many of whom have forsaken the habit because of their symptoms) is noteworthy.

TABLE VII.—*Smoking Habits by Age and Sex*

	Age Groups (in Years)					Total
	40–44	45–49	50–54	55–59	60–64	
Males:						
Non-smokers (%) ..	9	8	6	7	4	7
Ex-smokers (%) ..	14	14	18	23	20	18
Present smokers (%)	77	78	76	70	76	75
Total	100	100	100	100	100	100
Females:						
Non-smokers (%) ..	44	53	58	59	69	56
Ex-smokers (%) ..	9	6	9	11	9	9
Present smokers (%) ..	47	41	33	30	22	35
Total (%) ..	100	100	100	100	100	100

TABLE VIII.—*Smoking Habits and Bronchitis Prevalence Rates (Age-adjusted)*

	Non-smokers			Ex-smokers			Present Smokers			Total		
	No.	%B	%SD	No.	%B	%SD	No.	%B	%SD	No.	%B	%SD
Males	54	6	2	141	15	7	592	18	9	787	17	8
Females	442	5	3	70	13	7	270	12	4	782	8	3

Social Class

All but 2 of the 787 men were divided into social class according to their current or most recent occupation as set out in the Registrar-General's *Classification of Occupations* (1950). Their wives were put in the same social class groupings. Table IX shows that, in both sexes, the upward trend in bronchitis prevalence with descending social class is closely similar to the rise in the corresponding death-rate at ages 45–64 for men from 199 per 100,000 in social class I to 1,048 per 100,000 in social class V and from 35 per 100,000 in females in social class I to 87 per 100,000 in social class V.

TABLE IX.—*Social Class and Bronchitis Prevalence Rates (Age-adjusted)*

	Social Class											
	I		II		III		IV		V		Total	
	No.	%B	No.	%B	No.	%B	No.	%B	No.	%B	No.	%B
Males ..	29	6	151	11	379	18	131	19	95	26	785	17
Wives ..	21	—	82	7	218	10	78	10	43	15	442	10

Note: Excluding two males whose occupation was ill-defined.

Despite the smaller numbers of patients classified as " bronchitics " under the rigid criteria of the standard or syndrome diagnosis, the social-class distribution of the disease is still obvious in Table X. In other words, here is evidence that the social gradient in reported mortality from chronic bronchitis is unlikely to be due to differences in the diagnostic skills and habits of the doctors certifying death.

TABLE X.—*Social Class and Bronchitis Prevalence Rates (Age-adjusted)*

	Social Class								
	I and II			III			IV and V		
	No.	%B	%SD	No.	%B	%SD	No.	%B	%SD
Males	180	10	3	379	18	10	226	22	10
Wives	103	6	4	218	10	3	121	12	9

Note: Excluding two males whose social class was ill-defined.

Relationship Between Residence, Smoking Habits, and Social Class

There are significant differences between rural and urban males in their smoking habits, but, as Table XI shows, these differences in themselves cannot explain the rural : urban gradient in male morbidity. Similarly, Table XII shows that, although there are small but significant differences in smoking habits between the social classes, again these have no material effect on the social-class gradient in chronic bronchitis. These results in the age-group 40–64 thus confirm the independent effect of social class differences and cigarette smoking on bronchitis prevalence found in men over the age of 60 by Edwards *et al.* (1959).

TABLE XI.—*Male Bronchitis Prevalence Rates by Smoking Habits and Area of Residence (Age-adjusted)*

	Present Residence						Total	
	Rural Districts		Urban Districts and Municipal Boroughs		County and Metropolitan Boroughs			
	No.	%B	No.	%B	No.	%B	No.	%B
Non-smokers ..	16	7	23	10	15	—	54	6
Ex-smokers ..	27	11	64	7	50	27	141	15
Present smokers	115	13	268	18	209	24	592	18

TABLE XII.—*Male Bronchitis Prevalence Rates by Smoking Habits and Social Class (Age-adjusted)*

	Social Class						Total	
	I and II		III		IV and V			
	No.	%B	No.	%B	No.	%B	No.	%B
Non-smokers ..	16	—	29	9	9	12	54	6
Ex-smokers ..	42	6	62	15	36	26	140	15
Present smokers	122	13	288	20	181	22	591	18

Note: Excluding two whose social class was ill-defined.

Peak Flow Meter Readings

A major interest in this study was the evaluation of a simple test of respiratory function, applied by general practitioners, as an additional means of assessing respiratory disability.

The Wright peak flow meter was the only instrument readily available at the time of the survey which general practitioners could use to make some objective measure of ventilatory function. The use of this instrument requires the subject to co-operate fully in producing a maximum expiration, and a previous study has shown that a consistent observer bias may affect the result. Thus Fairbairn *et al.* (1961) found that three health visitors obtained readings systematically lower than those obtained by doctors on the same subjects on a different occasion. In the present survey, the general practitioners, who could not be given any detailed training in the use of this instrument, seemed to obtain systematically low readings. The results shown in Table XIII are much lower than those obtained in two previous surveys using this instrument. For males aged 45–54, for example, the value of 422 litres found by the practitioners is appreciably below the levels of 534 found by Higgins (1959) and 493 by Fletcher and Tinker (personal communication). In one of these surveys the mean of the three highest readings was taken, but an analysis of the present results showed that the convention used (averaging the last three readings) gave mean values only 3% lower than those obtained by the other method. With these reservations in mind, the figures obtained in the survey are none the less interesting.

TABLE XIII.—*Age Trends in Mean Flow Meter Readings (Litres/min.)*

		40–44	45–49	50–54	55–59	60–64	Total
Males	Others ..	486	447	432	411	388	435
	Bronchitics ..	390	338	304	241	288	293
	Total ..	479	435	409	374	361	411
Females	Others ..	339	332	314	306	298	318
	Bronchitics ..	261	250	293	214	256	250
	Total ..	334	327	313	298	293	313

As Table XIV shows, the Wright peak flow meters used in the survey give results which, although not adjusted for age, do discriminate to some degree between those patients whom their doctors reported as bronchitics and the remainder of the population surveyed. The average result in bronchitics is 32% below the result

TABLE XIV.—*Flow Meter Results in Bronchitis and Others*

Flow Meter Reading (litres/min.)	Males			
	Others		Bronchitics	
	No.	%	No.	%
0–	—	—	2	2
100–	12	2	30	23
200–	70	11	41	31
300–	172	27	31	24
400–	196	30	19	15
500–	127	20	7	5
600–	56	9	—	—
700–	5	1	—	—
Total	638	100	130	100

in the others. In Table XIII the steady downward trend in mean test result with increasing age indicates that the test will detect changes in function associated with ageing even in groups of apparently healthy subjects without bronchitis as diagnosed by these general practitioners. Among the bronchitics, the age trends in Table XIII show a rapid decline in early middle life with a hint of higher flow rates among those less seriously disabled bronchitics who have survived the age of 60 and more. An analysis of variance shows that these age differences are unlikely to be due to chance. Among the women the subjects with bronchitis had a mean flow rate 21% below those without it, and the decline with age among the latter was relatively slight. Among the female bronchitics it was irregular.

From the epidemiological point of view a simple functional test may be useful in giving independent evidence, corroborative or otherwise, about the level of respiratory disability in contrasted population groups. Table XV, for example, shows that the mean test results achieved by non-smokers, ex-smokers, and present smokers are consistent with the ranking of the clinical

TABLE XV.—*Peak Flow Meter Results According to Smoking Habits (Age-adjusted Score in Litres)*

	Males	Females
Non-smokers	448	318
Ex-smokers	417	300
Present smokers: 1–14 per day	412	314
Present smokers: 15–24 ,, ,,	399	310
Present smokers: 25+ ,, ,,	398	265

estimates of the prevalence of bronchitis in these groups. These findings are similar to the differences in indirect maximum breathing capacity between smokers and non-smokers reported by Higgins (1959) in non-mining males aged 55–64 and the decline in performance on the Goldsmith peak flow meter in smokers noted by Flick and Paton (1959).

In women, there is no difference between non-smokers and smokers of less than 25 cigarettes per day. The six women who smoked most heavily had a reduced value and the ex-smokers also showed reduced values. Fletcher *et al.* (1959) found no difference in indirect M.B.C. between female smokers and non-smokers.

The corresponding comparison between men and women living in different parts of the country is seen in Table XVI to show some consistency with the results in Table VI, but the difference between rural and city men is small and not technically significant. Although

TABLE XVI.—*Peak Flow Meter Results According to Present Residence (Score in Litres)*

Area	Males	Females
Rural	419	313
Urban and municipal	418	317
County and metropolitan	398	310

comparisons between practices may be particularly affected by observer variation, these results would suggest that urban:rural differences in functional disability are less than those associated with cigarette smoking.

It thus appears that despite the systematically low levels of expiratory flow rates found by the doctors in our survey the peak flow meter revealed trends in the male bronchitics such as would be expected, and it appears to have fulfilled a useful function. Among the women the trends were irregular and confusing. Some irregularity may result from the smaller numbers involved. Experience shows, however, that women are less suitable subjects than men in the performance of a test that requires maximum effort.

Discussion

In this report we have not attempted to present a complete analysis of all the data collected in the survey. But we hope to have shown the potentialities as well as the limitations of this novel approach in general-practitioner research. Given the help of the administrative officers at all levels in the structure of the National Health Service, a large survey of the prevalence of a chronic disabling disease among a randomly selected sample of the populations served by selected general practitioners has been shown to be possible. Clinical histories of respiratory symptoms and the personal characteristics such as residence and smoking which may be related to them can also be elicited by means of a standardized questionary so that some countrywide uniformity in the data collected can be ensured.

Impaired ventilatory capacity was effectively demonstrated by general practitioners using a simple test of respiratory function. The levels they obtained were consistently lower than those obtained by specialist field workers; but the trends in relation to age, sex, and smoking habits in men were consistent with those of the others.

The patterns of the distribution of chronic bronchitis prevalence based on practitioners' diagnosis are in broad agreement with those given by a "standard diagnosis" based on the presence of defined symptoms. In whichever of those two ways it is defined, chronic bronchitis as found in this survey shows the same relationship to age, sex, social class, and place of residence as the mortality or morbidity rates for this disease recorded in the national vital statistics. It seems unlikely, therefore, that the social or urban:rural gradients already reported in official and other reports are due to regional or other differences in diagnostic habits or standard of certification. Indeed, the use of the "standard" diagnostic criteria showed a greater rural:urban gradient than these reports suggest.

If this sample can be taken as fairly representative of the country as a whole, the striking social pattern seen in mortality data is reflected in morbidity; and these social-class differences in prevalence cannot be attributed to differences in smoking habits. Here again standardization of diagnosis has emphasized the importance of the social-class gradient in the disease. The sex difference, on the other hand, may be largely due to the divergence in smoking habit.

The low male:female ratio of morbidity in our survey compared with that reported from chest clinics and in mortality from bronchitis is interesting and suggests that fewer women than men are referred to hospitals for bronchitis and that the case fatality rate may be lower in women than in men. The relatively small rural:urban gradient of bronchitis prevalence in women and the smaller differences in peak expiratory flow rate between women with and without bronchitis and between women smokers and non-smokers all suggest that chronic bronchitis as diagnosed in women by the practitioners in our survey differs in important clinical respects from that seen in men.

In so far as they have confirmed previous findings, resolved some doubts and suggested explanations for

some of the relations between disability and death from chronic bronchitis and personal habits or environment, these results may be held to justify this approach in research by general practitioners. Much remains to be done—for example, by relating the findings to national vital statistics and other surveys—but the prospect for such developments in general-practitioner surveys within the National Health Service seems promising.

Summary

Under the direction of the Research Committee of Council of the College of General Practitioners and with help from the Ministry of Health, 92 general practitioners working within the National Health Service conducted a survey of respiratory symptoms and disability among a randomly selected sample of men and women on their practice lists. These practices were scattered throughout Britain in both urban and rural areas. Of the 1,630 individuals selected for interview and still alive or available in the practice areas, 1,569 (94%) (787 men and 782 women between the ages of 40 and 64) were seen. The wives of 442 of those selected men were also interviewed.

Respiratory histories were recorded on a standard questionary, and ventilatory capacity was usefully assessed by the Wright peak flow meter.

An analysis was made of the frequency of "chronic bronchitis," diagnosed by the participating doctors after using these standard methods of clinical inquiry, in relation to age, sex, smoking habits, place of residence, and social class. The prevalence of chronic bronchitis was 17% in men and 8% in women, and, among men, ranged between 6% for non-smokers to 18% for smokers, from 12 to 23% between country and city, and from 6 to 26% between social classes I and V. The results in women were less regular. Similar analyses of the distribution of cases diagnosed as "bronchitis" on the presence of winter morning phlegm, chest colds, and breathlessness confirmed that both these results and the social and regional pattern of mortality and morbidity seen in national vital statistics are unlikely to be due to variations in diagnostic skill and certification practice.

The results are compared with previous mortality and morbidity data and with findings in other field surveys. Their value in amplifying and explaining the relationship between bronchitis prevalence and—for example, smoking and residence—has been shown.

The evidence provided by this study supports the following conclusions in this respect.

1. The significant differences in smoking habits found between town and country males are not enough to explain the urban: rural gradient in male morbidity.

2. Small differences in smoking habits have no material effect upon the social-class gradient in chronic bronchitis prevalence.

3. Sex differences in prevalence rates, however, may be largely explained by differences in cigarette consumption; but the lower sex-ratio found in random samples of practice populations compared with that in—for example, death rates and admission rates to hospital—strongly suggests the lesser severity of chronic bronchitis in women. The results of applying this peak flow meter test of respiratory function support that suggestion.

The contribution which this form of general practitioner research may make to an understanding of current trends in disability or death from chronic bronchitis is briefly discussed.

The College of General Practitioners is indebted to the Nuffield Provincial Hospitals Trust for a grant which defrayed the expenses of this investigation. The analysis of results was carried out in the Department of Medical Statistics and Epidemiology at the London School of Hygiene and Tropical Medicine, while a subcommittee (Drs. C. M. Fletcher, J. Fry, and N. C. Oswald and Professor D. D. Reid) was responsible for the preparation of the report. The working party wishes to express its thanks to the patients and the practitioners concerned and to the Ministry of Health and the executive councils for their help.

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CHEMOTHERAPY OF BRONCHITIS

INFLUENCE OF PENICILLIN AND TETRACYCLINE ADMINISTERED DAILY, OR INTERMITTENTLY FOR EXACERBATIONS

A REPORT TO THE RESEARCH COMMITTEE OF THE BRITISH TUBERCULOSIS ASSOCIATION BY ITS BRONCHITIS SUBCOMMITTEE*

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An investigation by this Subcommittee carried out from January to April, 1959, showed that the number of working days lost as a result of bronchitis was halved by the daily administration of antibiotic capsules compared with a similar group of patients taking inert capsules (British Tuberculosis Association, 1960). The antibiotics employed were tetracycline, 250 mg. twice daily, and penicillin-V potassium, 312 mg. twice daily. The results are summarized as follows:

	Mean Time Off Work per Day at Risk	Average Time Off Work per Patient
Penicillin group	0·06 day	6·8 days
Tetracycline group	0·06 ,,	7·5 ,,
Control group	0·12 ,,	14·2 ,,

The variable nature of the response was such that the observed difference between the two antibiotic groups was compatible with either drug having an advantage of some four working days over the other. The number of bronchitic exacerbations appeared to be unaffected by treatment. Bearing in mind the comparatively small dose of tetracycline, it was thought that the main action of both antibiotics had been to suppress infection due to pneumococci, neither regimen having had much effect on *Haemophilus influenzae*. In an attempt to clarify this point it was thought that a subsequent investigation should include a study of the bacteriology of the patients' sputa.

The purpose of the present investigation was, firstly, to ascertain whether these findings held good for another winter and to compare the value of antibiotics administered prophylactically each day throughout the winter with an alternative prophylactic regimen in which antibiotics were to be given in higher doses for short periods at the onset of symptoms usually leading to a bronchitic exacerbation. Secondly, it was proposed to make a more detailed bacteriological study based on sputum specimens examined under research conditions before, during, and after the end of such treatment.

*Members of the Subcommittee are: Dr. P. Baldry (honorary secretary), Dr. J. R. Bignall, Dr. R. S. Francis, Dr. S. W. A. Kuper, Dr. G. P. Maher-Loughnan, Dr. Robert May, Dr. E. N. Moyes, Mr. P. D. Oldham, Dr. Hugh Ramsay (chairman), and Dr. C. C. Spicer. The trial was co-ordinated by Dr. R. S. Francis, the bacteriology by Dr. R. May, and Dr. C. C. Spicer was reponsible for all statistical aspects.

Methods

In view of the improvement in health which resulted from antibiotic medication in the previous trial, the inclusion in the second trial of a group of patients receiving nothing but an inert substance was considered inadmissible on ethical grounds. The regimens adopted were as follows, being maintained throughout the period of the trial.

Regimen	Daily Capsules. Dose: One Capsule before Breakfast and on Retiring	Intermittent Capsules. Dose: 2 Capsules t.d.s for 3 Days, then 1 t.d.s. for 3 Days
A	Starch	Penicillin
B	Tetracycline	Starch
C	Penicillin	Starch
D	Starch	Tetracycline

Patients having daily antibiotic capsules were given inert capsules intermittently, and vice versa.

A list of 12 treatments—three of each regimen—was drawn up at random, for each clinic separately. Chest physicians were asked to recruit 12 patients and to forward their names. As these were received they were allocated in turn to the list of treatments. Some clinics recruited fewer than 12 patients, so that there was some imbalance finally in the total number of patients on each regimen.

Daily capsules were pink and indistinguishable from each other. They were to be taken every day throughout the trial, even when "intermittent" capsules were also being taken. The doses of the daily antibiotics were as in the previous trial—namely, penicillin-V potassium, 312 mg. b.d., or tetracycline, 250 mg. b.d.

"Intermittent" capsules (brown) were also indistinguishable from each other. They were presented in bottles each containing sufficient capsules (27) for six days' medication. Each patient was to start taking these at the first appearance of symptoms, which in his particular case were usually followed by an exacerbation of bronchitis. The dose of antibiotics to be taken intermittently was either (1) penicillin-V potassium 624 mg. (equivalent to 1 million units by injection) thrice daily for three days, followed by 312 mg. (equivalent to half a million units by injection) thrice daily for a further three days, or (2) tetracycline 500 mg. thrice daily for three days, followed by 250 mg. thrice daily for a further three days.

Apart from the addition of the intermittent medications, the trial was conducted along lines very similar to that of January–April, 1959. The main difference was that in the second trial the bottles of capsules were distinguished by a code letter whereas in the first trial code letters were unnecessary and were not used.

Central Organization

Penicillin was provided by Messrs. Eli Lilly and tetracycline by Messrs. Lederle. Both the antibiotics and the inert preparation (starch) were encapsuled and bottled by Messrs. Eli Lilly, who dispatched to each

clinic a box containing one large jar of daily capsules for each patient, labelled with the appropriate letter, together with four small bottles of "intermittent" capsules for each patient, similarly labelled. The identity of the regimens A, B, C, and D were not known to any of those partaking in the trial or to any of the members of the Bronchitis Subcommittee until after the results had been fully analysed.

Graduated sputum pots, specially printed patients' diaries, and instruction sheets were also sent to each clinic, together with a letter to the local bacteriologist giving details of the investigations required in relation to sputum cultures.

Chest Clinic Organization and Clinical Material

The selection of patients for the trial was based on criteria almost identical with those of the first trial, as follows: Patients should be men, preferably wage-earning, aged 30–65, in employment, and with a history of winter cough and sputum for the past three years. During this time they should have been off work at least twice because of bronchitis with purulent sputum, and they must be reasonably intelligent and willing to co-operate even if they thought the capsules were unhelpful.

Patients were not suitable for the trial if their main symptom was wheezing, if they had been in heart failure, or if radiographic changes other than those of bronchitis and emphysema were present. Also excluded from the trial were those known to be sensitive to penicillin and those likely to be off work because of some other disability.

At a preliminary interview the purpose of the investigation was explained to the patients, who were instructed in its routine, the keeping of the diaries, and the importance of consulting their general practitioners when necessary. They were given an instruction sheet, a bottle of daily capsules, and two bottles of capsules for intermittent use. Arrangements were made for the latter to be replaced as soon as they were used up.

As in the previous trial, the following definition of "bronchitic exacerbation" was adopted: "An increase in cough with the appearance of pus in the sputum or an increase in the amount of pus over the amount usually present."

Chest physicians were asked to interview the patients once a month and to make entries on a form relating to the number of bronchitic exacerbations, pneumonic episodes, or "other respiratory" disorders developing, and the number of days on which patients were consequently unfit for work. Days spent in hospital were indicated separately. They were also asked to record symptoms attributed to the capsules, and to note any omissions of treatment together with any chemotherapy prescribed by the general practitioners. The co-operation of the latter was obtained beforehand, and practitioners remained in charge of the patients, being free to prescribe any treatment other than *prophylactic* antibiotics.

In his monthly assessments the chest physician could call on the following sources of evidence:

1. The ordinary methods of history-taking and examination.

2. Examination of the sputum produced that morning, which the patient was asked to bring with him.

3. The patient's diary, in which was recorded the daily colour and approximate volume of the sputum and a note on his general condition (better, the same, worse, or much worse than usual); the 24-hour volume and colour of sputum on Sundays and all days when off sick; the dates of stopping and resuming work; and, finally, any antibiotic treatment received from the general practitioner, who was asked to make such entries whenever applicable.

4. Health visitors' reports, based on two home visits a month, the purpose of which was to report on the patient's health, sputum state, work status, toxic symptoms, and whether or not capsules were being taken, together with any relevant comment.

At the end of the trial, weekly tobacco consumption was recorded; all chest physicians' reports, diaries, and health visitors' reports were then forwarded for analysis.

Laboratory Organization

The collection of sputum specimens from patients and their delivery to the laboratory was organized by the chest physicians at each clinic. Three sputum examinations were carried out during the trial: (*a*) during the week preceding its commencement, (*b*) during a week in the middle of the trial, and (*c*) during the second week after the end of the trial. On each occasion three specimens of sputum from each patient were cultured, in order to reduce the sampling errors inherent in the examination of single specimens (May, 1953). The three samples were all expectorated by the patient on the same day.

The arrangements for bacteriological examination of the sputa were as follows.

1. *Clinics in the London Area.*—The sputa of patients attending 12 clinics in or near London were delivered by hand on the day of expectoration to the bacteriology laboratory of the Institute of Diseases of the Chest, where all cultures were carried out.

2. *Provincial Clinics.*—Sputum examinations were undertaken on the patients attending 24 clinics outside London. The examinations were carried out in the bacteriology laboratory normally serving each clinic. As before, the cultures were made on the day of expectoration of the sputum.

This procedure was not ideal, since there could be no absolute standardization of culture techniques. However, all bacteriologists were asked to adopt, if possible, the method used at the Institute of Diseases of the Chest (see below), and in fact 20 of the 24 did so. The results suggest that errors introduced from this source were not appreciable.

Sputum Culture Technique.—The method used for all specimens from the London clinics and for those from the majority of provincial ones was the pancreatin liquefaction technique described by Rawlins (1953). Briefly this consists in mixing the sputum with an equal volume of 1% pancreatin solution buffered to *p*H 7.6 and incubating in a water-bath at 37° C. until liquid. The standard primary culture medium was blood-agar, additional special media being used as appropriate for the isolation and identification of individual bacterial species. Attention was paid especially to the isolation of *H. influenzae* and pneumococci.

Sensitivity of Bacteria to Antibiotics.—In order to maintain a standard technique for sensitivity-testing, all tests were carried out in one laboratory (Institute of Diseases of the Chest), to which cultures of strains isolated in provincial laboratories were sent. Strains of *H. influenzae* only were investigated. The pneumococcus was accepted as being invariably sensitive to the drugs used in the trial (penicillin and tetracycline).

Sensitivity was estimated by titration on a solid medium (agar containing X and V factors) in Petri dishes. The organisms were "spotted" on to a series of plates containing 0.3, 0.6, 1.25, 2.5, and 5 units of penicillin per ml. respectively, and on to a second series containing 0.3, 0.6, 1.25, 2.5, and 5 μg. of tetracycline per ml. respectively. A control plate containing no antibiotic was included in each series, and a standard test strain of *H. influenzae* was inoculated with each batch of organisms tested. By this method 16 strains could be tested simultaneously on each set of plates. The "sensitivity" of each strain was recorded as the lowest concentration of antibiotic causing complete inhibition of growth.

Results

The trial started on November 16, 1959, and ended on April 16, 1960—a total of 153 days. The reports received were on the whole clear-cut, but where information was equivocal or incomplete it was necessary to consult the diaries or health visitors' reports to supplement factual information such as the date of a patient's return to work. This procedure was not often invoked, but it was always carried out according to a set of pre-established rules. Particular care was taken to establish whether a patient was exposed to risk according to the terms of the trial. Thus, an exacerbation of bronchitis or a pneumonic episode could be regarded as relevant only if the patient was at work and taking his daily capsules at the time of onset. He could not "qualify" for a second attack until he had returned to work after the first. Days on which a patient omitted his daily capsules were counted as "out of trial," since he was not fulfilling the conditions of the experiment. This ruling led to an anomaly in the case of patients admitted to hospital, when daily capsules were often discontinued, such days also being "out of trial." Fortunately the numbers involved were small, and even if those days were included in the totals lost by each group the results are not affected. These cases are fully discussed later.

Physicians in 51 chest clinics in urban and rural areas throughout England, Wales, and Scotland took part in the trial, and the total number of patients starting the trial was 551. Of these, 10 refused to co-operate and never reported for subsequent interview; in six cases the data were inadequate or conflicting, and two cases had to be rejected because, contrary to the agreed conditions of the trial, their general practitioners treated them for prolonged periods with a daily antibiotic prescribed by themselves. A total of 18 patients have therefore been excluded from further consideration. Table I shows their distribution in the four regimens.

The number of patients available for study is therefore 551 less 18, or 533. It was a condition of the trial that all patients should be at work; in fact, 14 were unemployed throughout, and although their experience can be taken into account when considering side-effects of treatment they clearly cannot be included in the main analysis, which is concerned with days of unfitness for work. The total number of patients available for statistical study is therefore 533 less 14, or 519, which represents 94% of those entering the trial. Table I summarizes the position.

TABLE I.—*Clinical Material*

	Totals	Regimen			
		Inter. Pen.	Daily Tet.	Daily Pen.	Inter. Tet.
No. entering trial, Nov. 16, 1959 ..	551	133	135	140	143
Not available for study:					
(1) Uncooperative: no data ..	10	2	2	2	4
(2) Insufficient or conflicting data	6	1	3	0	2
(3) Prophylactic chemotherapy from G.P.	2	0	2	0	0
Remainder available for study ..	533	130	128	138	137
Patients unemployed throughout	14	1	3	3	7
Available for statistical analysis ..	519	129	125	135	130

Statistical Analysis of Results

Some lack of balance in the distribution of patients was inevitable, since not all clinics could fill their quota of suitable patients. Experience with the previous trial had shown that this was not a serious fault, as the errors introduced by an uneven distribution of the regimens among the clinics are negligible compared with the uncontrolled variations between patients. All estimates of treatment effects are based on the days off work per 100 days exposed in the trial averaged over all clinics. The corresponding standard errors include the difference between clinics as a source of variation.

Information on four variables used to check the randomization is given in Table II. It will be seen that the average ages of patients, their smoking habits, and the proportions working indoors are very similar. The average days withdrawn from the trial for reasons unconnected with respiratory disease are also similar. None of the differences between the treatment groups are statistically significant, and they are in fact about what would be expected from the known variations between patients. Information was also asked for on body weight, but this was very incompletely reported and has not been used for comparative purposes.

TABLE II.—*Average Values of Some Characteristics of Patients in the Four Regimens*

Characteristic	Inter. Pen.	Daily Tet.	Daily Pen.	Inter. Tet.
Average age (years)	52·6	53·9	53·0	53·4
,, days withdrawn from trial ..	10	12	11	11
,, tobacco smoked (cigs./wk.)	59	59	63	61
Proportion of indoor workers ..	61%	69%	60%	63%

The main results of the trial are shown in Table III, which gives the average number of days off work from bronchitis per 100 days exposed for the four regimens.

TABLE III.—*Mean Days Off Work Per 100 Days Exposed, From Bronchitic Exacerbations, With Standard Errors of Means and Numbers of Patients on Which They Are Based*

Regimen	Mean Days Off Work per 100 Exposed to Risk	S.E. of Mean	No. of Patients
Intermittent penicillin ..	8·311	1·373	129
Daily tetracycline ..	4·039	0·911	125
,, penicillin	8·127	1·652	135
Intermittent tetracycline	9·339	1·641	130

It can be seen that the group receiving daily tetracycline had about half as many days off as those on the other three regimens. With the use of the test for the deviation of the smallest of four averages in *Biometrika Tables for Statisticians* (1958, Table 26), it was found that the effect of daily tetracycline is significant statistically ($P \leqslant 0.01$). The differences between the other regimens are not significant.

Information was also available on the days off work due to pneumonia and other respiratory diseases. The number of patients having an attack of pneumonia was

too small to be worth detailed consideration, but the average days lost from other respiratory disease in the four groups are given in Table IV. The very considerable excess of days off from other respiratory disease in the group receiving penicillin intermittently is highly

Table IV.—*Mean Days Off Work Per 100 Days Exposed, From Respiratory Infections Other than Bronchitis or Pneumonia*

Regimen	Mean Days Off Work per 100 Exposed to Risk	S.E. of Mean	No. of Patients
Intermittent penicillin ..	1·756	0·640	129
Daily tetracycline ..	0·710	0·270	125
,, penicillin	0·523	0·201	135
Intermittent tetracycline	0·570	0·214	130

significant statistically, and it seems probable that the other three regimens were able to produce a reduction, since it is unlikely that the penicillin was actually harmful.

In the first trial it was found that neither daily tetracycline nor daily penicillin reduced the actual number of bronchitic attacks. The differences in the average number of attacks on each regimen are not significant, though the two groups on daily medication do have rather smaller averages than the others.

It is of interest to consider the frequency with which intermittent medication was resorted to by patients in the different groups. A true prophylactic effect of intermittent medication would reduce the actual number of attacks, since the patients were supposed to take their capsules when they felt an attack coming on. However, the number of such courses taken was almost equal to the number of attacks, the proportions followed by an attack in the four groups being: intermittent penicillin, 87% ; daily tetracycline, 90% ; daily penicillin, 83% ; and intermittent tetracycline, 82%.

Clearly there was little difference between the inert tablets and the antibiotics. A true control group having no form of medication would be required to settle the matter, but it appears from these findings that the effect of taking capsules was on the course of the attack once it had developed.

Information on the number of attacks for which the patient sought treatment from his general practitioner was recorded. The average number of these per patient in the four groups was: intermittent penicillin, 0.25 ; daily tetracycline, 0.10 ; daily penicillin, 0.10 ; and intermittent tetracycline, 0.13.

The relatively large number of these treatments among patients taking penicillin intermittently is significant statistically and might be of importance when it is remembered that this group also had an excess of other respiratory disease. These differences could be due either to the general inadequacy of penicillin when taken intermittently or, possibly, to the concentration of some particular type of patient in this group as a chance consequence of the randomization procedure.

Symptoms Attributed to the Capsules

Most of the side-effects attributed to the capsules occurred for a short period only at the beginning of the trial. In some instances symptoms were reported occasionally throughout the trial, and in only a small number of cases were they said to be persistent. Only 10 patients refused to take their capsules because of side-effects, which were attributed to starch in six cases, penicillin in three cases, and tetracycline in one case.

The proportions of patients affected by the individual antibiotic capsules were as follows: intermittent penicillin, 12% ; daily tetracycline, 27% ; daily penicillin, 27% ; and intermittent tetracycline, 17%. They are effectively equal when sampling variation is taken into account. Mild gastro-intestinal symptoms were in the majority. A few patients developed skin rashes and there were a few complaints of headache and attacks of asthma. Further details are recorded in Table V.

Table V.—*Patients Having Symptoms Attributable to Capsules*

Capsules to which Symptoms Attributable	No. of Patients in Whom Symptoms were Reported			No. of Patients Refusing to take Capsules
	Total	Occasional Symptoms	Persistent	
Daily penicillin ..	27	19	8	2
,, tetracycline	27	19	8	1
,, starch* ..	23	17	6	3
,, starch† ..	28	21	7	3
Intermittent penicillin	12	7	5	1
Intermittent tetracycline	17	14	3	0
Intermittent starch‡	9	9	0	0
,, starch§	14	9	5	0

* With penicillin intermittently. † With tetracycline intermittently. ‡ With penicillin daily. § With tetracycline daily.

Patients Admitted to Hospital

Only 15 patients were reported to have been admitted to hospital, several of these having had cardiac complications of respiratory disease. Only six of the patients are known to have continued taking daily capsules while in hospital, and three were admitted to hospital during periods when they were technically " out of trial " because of a temporary failure to fulfil the criteria of exposure to risk. In fact, two patients who died were in this latter group. For these reasons, days off work in hospital were not included in the analysis, the validity of the results being unaffected since inclusion of these patients would make virtually no difference to the average days unfit for work per 100 days' exposure, each regimen being affected about equally.

Table VI shows the numbers of patients in each regimen who were admitted to hospital together with the duration of stay. No clear advantage can be attributed to any single regimen.

Table VI.—*Patients Admitted to Hospital*

Regimen	No. of Cases	Average Days in Hospital	Deaths
Intermittent penicillin ..	5	29	1 after 46 days
Daily tetracycline ..	2	17	
,, penicillin	2	21	
Intermittent tetracycline	6	28	1 ,, 6 ,,

Deaths

There were six deaths among the 533 patients available for study. Two were in the intermittent tetracycline group, three were in the daily penicillin group, and one was receiving daily tetracycline. The following are brief case histories:

Regimen—Intermittent Tetracycline

1. H. W., No. 15/12, aged 51. This patient was off work continuously from two weeks preceding the beginning of the trial and is included in the " unemployed " group in Table I. He was admitted to hospital suffering from incapacitating emphysema on January 14, 1960, his sputum having dried up after the trial had started. He died in hospital on January 20 of respiratory insufficiency and his days off work were not included in the main analysis.

2. C. B., No. 43/1, aged 57. This patient died at home on December 23, 1959, before his first assessment. So far as we know, he fulfilled the conditions of the trial up till death, which was certified at necropsy as being caused by "cor pulmonale due to an acute flare of chronic bronchitis and emphysema." His days off work are included in the statistical analysis.

Regimen—Intermittent Penicillin

1. L. S., No. 35/9, aged 60. This patient died on the fifth day of the trial. He started daily capsules on November 16, 1959, and intermittent ones on November 17. He died on November 20 from "bronchitis," and his four days of exposure have been included in the analysis.

2. A. B., No. 06/1, aged 61. This patient died of cor pulmonale due to chronic bronchitis and emphysema on December 16, 1959, and his 31 days' exposure have been included in the analysis.

3. B. P., No. 32/8, aged 55. This patient was exposed to risk for 33 days, which have been included in the analysis. He stopped work because of an attack of "other respiratory" disease, and, while thus temporarily not exposed to risk, he developed bronchitis, for which he was admitted to hospital on February 24, 1960, where he died on April 11.

Regimen—Daily Tetracycline

G. B., No. 5/1, aged 47. This patient was exposed for 45 days till sudden death on December 15, 1959, certified by the general practitioner as due to cerebral haemorrhage.

The number of deaths is so small and the variation between patients so large that no useful comparisons can be made between the regimens on a mortality basis.

Bacteriological Results

The total isolation rates of *H. influenzae* differed slightly in London and the provinces. Combining all regimens and all phases of the trial, *H. influenzae* was isolated in 141 (41%) of 343 patient-examinations in London, compared with 190 (26%) of 730 patient-examinations in the provinces. This difference may represent an actual difference in the prevalence of the organism in London and the provinces, but a more likely explanation is that it results from the differences in technique used in various laboratories. For example, no *H. influenzae* was isolated from any patient at any stage of the trial in one laboratory, in which cultures were made by dipping a throat swab into the sputum and inoculating on a blood-agar plate. Since the clinic served by this laboratory was near London, close to the clinics where *H. influenzae* was isolated frequently, it seems unlikely that these patients were in fact free from this organism. Although there were a few other examples of laboratories with low isolation rates for *H. influenzae*, in the majority they were similar to those in London. The geographical distribution of the laboratories with low rates was haphazard and did not suggest that *H. influenzae* was in fact less prevalent in certain parts of the country. It seems reasonable to conclude, therefore, that the difference between the isolation rates for London and the provinces was the result of differences in the technique used for sputum culture. Therefore the tota' isolation rates of *H. influenzae* from all clinics combined are probably rather lower than the true prevalence of the organism.

In contrast, the isolation rates for pneumococci were very similar in the two groups of clinics. In London, pneumococci were isolated from 92 (27%) of 343 patient-examinations (all phases of the trial combined), while in the provinces they were found in 213 (29%) of 730 patient-examinations. In general, the pneumococcus is easier to isolate from sputum than *H. influenzae* and differences in culture technique are unlikely to be important; hence the similarity of the results in the two groups of clinics.

Tables VII and VIII show the isolation rates for *H. influenzae* and pneumococci respectively within the four regimens. At the beginning and end of the trial

TABLE VII.—*Isolation Rates of H. influenzae From Sputum in Different Regimens. (All Clinics Combined)*

	Regimen			
	Inter. Pen.	Daily Tet.	Daily Pen.	Inter. Tet.
Beginning of trial:				
No. of patients	101	98	103	103
H. influenzae isolated ..	26 (26%)	28 (29%)	31 (30%)	33 (32%)
Middle of trial:				
No. of patients	92	83	91	88
H. influenzae isolated ..	37 (40%)	13 (16%)	39 (43%)	25 (28%)
End of trial:				
No. of patients	83	75	81	79
H. influenzae isolated ..	25 (30%)	20 (27%)	28 (35%)	25 (32%)

TABLE VIII.—*Isolation Rate of Pneumococci From Sputum in Different Regimens. (All Clinics Combined)*

	Regimen			
	Inter. Pen.	Daily Tet.	Daily Pen.	Inter. Tet.
Beginning of trial:				
No. of patients	101	98	103	103
Pneumococci isolated ..	41 (41%)	41 (42%)	38 (37%)	46 (45%)
Middle of trial:				
No. of patients	92	83	91	88
Pneumococci isolated ..	20 (22%)	10 (12%)	14 (15%)	27 (31%)
End of trial:				
No. of patients	83	75	81	79
Pneumococci isolated ..	23 (28%)	11 (15%)	11 (14%)	23 (29%)

the isolation rate of *H. influenzae* was substantially the same among patients in all four groups, but there were some divergences in the middle of the trial. In the intermittent penicillin group and the daily penicillin group the isolation rate rose by nearly 50%; in the daily tetracycline group it fell by nearly 50%; while in the intermittent tetracycline group it remained unchanged. These differences are in fact not statistically significant at the 0.05 level, but the trends are clear. The most likely explanation is that there was a rise in the carrier rate of *H. influenzae* in the middle of the trial (February) and that this was unaffected by either of the penicillin regimens. Daily tetracycline, however, caused a reduction in the carrier rate, while intermittent tetracycline was able to prevent only the seasonal rise. At the end of the trial the isolation rates were the same as those at the beginning. This was not unexpected, since the cultures were made one to two weeks after the end of chemotherapy, by which time *H. influenzae* would have been expected to reappear in those patients in whom it had been temporarily suppressed.

The behaviour of pneumococci (Table VIII) contrasted with that of *H. influenzae*. The isolation rates were substantially the same in all regimens at the beginning of the trial, but all were reduced in the middle. This reduction was very marked in the two groups receiving daily antibiotics, being slightly greater in the patients having daily tetracycline. The carrier rate was reduced by about 50% in the group receiving intermittent penicillin, while in the intermittent tetracycline group it fell by about 33%. At the end of the trial isolation rates did not return to the pre-trial figures but remained approximately the same as those in the middle. This is in accordance with the known tendency of chemotherapy to eradicate pneumococci completely. These

organisms seldom reappear as quickly as those of *H. influenzae*.

No change in the sensitivity pattern as regards penicillin was observed in any regimen, but in the daily tetracycline group there was a slight trend towards increased tetracycline resistance at the end of the trial. This trend, however, was very small and of no significance statistically.

Full details of the bacteriological findings in this trial together with certain other aspects not given in the present report will be published elsewhere.

Discussion

The main finding of the present trial is the existence of a clearly defined superiority of the daily tetracycline regimen over the other three regimens. This is in contrast to the result of the previous experiment, in which daily penicillin and daily tetracycline appeared equally effective in halving the days lost from work compared with the control group.

There are two obvious possible explanations of this discrepancy. Either the large sampling errors of the estimated effects of the regimens are responsible or there was a difference in the aetiology of bronchitic exacerbations in the two years of the trials. The corresponding results of the two experiments in terms of mean days off per 100 exposed were:

	Tetracycline	Penicillin	Difference (Tet. minus Pen.)
First trial	8·38	6·57	+1·81±2·34
Second trial	4·04	8·13	−4·09±2·04

The difference between the two trials in the relative effects of daily tetracycline and penicillin does not quite reach statistical significance, and it would be legitimate on this evidence alone to regard the superiority of the daily tetracycline regimen as unproved. However, the difference is large and there is good reason to believe that tetracycline, by virtue of its ability to suppress both *H. influenzae* and pneumococci, might be superior to penicillin. It is probably most reasonable to conclude that the relative value of the two antibiotics differs from year to year according to the prevalence of each organism. It is difficult to see how the true position can be made clear without repeating the trial on about the same scale over a period of several years. Experience with other bacteria shows that the prevalence of an organism may vary from one year to another, and in the present case this could be of particular importance since it is probable that the haemophilus is susceptible virtually only to tetracycline. In addition to this it is known that the incidence of bronchitic exacerbations is considerably affected by weather conditions, which may interact in a complex way with the bacterial invaders: the weather during the first trial was much more severe than that during the second.

In the present trial, ethical considerations precluded the inclusion of a group of patients having both daily and intermittent inert capsules, and for this reason the regimens adopted can be assessed only in relation to each other. It is of interest, however, that in the trial of January to March, 1959, the control group lost an average of 12 days per 100 exposed, a much higher figure than any of the groups in the present experiment.

Clinicians experienced in the use of self-administered broad-spectrum antibiotics by chronic bronchitics at the onset of their attacks may be surprised at the comparatively poor results in this trial of antibiotics taken in this fashion. Scrutiny of the reports on individual patients showed that in fact they had not always followed the instructions concerning intermittent medication. Sometimes they had allowed attacks to become well established before taking their capsules, and in some cases had failed to take them at all. The circumstances of a centrally co-ordinated "blind" clinical trial differ considerably from those of ordinary medical practice, and in this particular instance it would not be justifiable to conclude that self-administered antibiotics taken at the start of symptoms leading to bronchitic exacerbations will in all circumstances give unsatisfactory results compared with daily administration.

Apart from the relative expense of the two antibiotics the experience of both trials suggests that daily tetracycline is the treatment of choice, since it has not been significantly worse than penicillin and it may be better. However, in view of the high cost of tetracycline further investigation is desirable to determine those conditions under which penicillin may be as good as tetracycline, so that a more economical form of prophylaxis can be worked out.

Summary

A second controlled investigation was carried out during the winter of 1959–60 in an attempt to establish the value of penicillin and tetracycline when administered to chronic bronchitics in widely scattered areas of England, Wales, and Scotland. Patients were allocated at random to one of the four regimens: (1) Tetracycline 250 mg. twice daily throughout the trial. (2) Penicillin-V potassium 312 mg. twice daily throughout the trial. (3) Tetracycline 500 mg. thrice daily for three days at the onset of symptoms followed by 250 mg. thrice daily for three days. (4) Penicillin-V potassium 624 mg. thrice daily for three days at the onset of symptoms, followed by 312 mg. thrice daily for three days.

Daily treatment with tetracycline led to a significant decrease in working days lost from bronchitis compared with the other three regimens. Probable explanations for these findings are discussed, with particular reference to the results of the previous winter's investigation, in which daily tetracycline and daily penicillin had been found equally effective.

Side-effects of the antibiotics presented no special problems.

The bacteriological aspects of the investigation showed that the prevalence of pneumococci was reduced by about 75% when either antibiotic was given daily and to a lesser degree when they were given intermittently. The carrier rate of *H. influenzae*, however, was reduced only in patients receiving daily tetracycline.

We are indebted to Mr. H. R. Simpson, of the statistics department, Rothamsted Experimental Station, for his help in the analysis of this trial on the electronic computer there, and to Miss Molly Fretton for statistical assistance. We are grateful to the North-East Metropolitan Regional Hospital Board for facilitating the participation of Dr. R. S. Francis, together with a grant for expenses; to Derrick May, Brian Gibbins, and Doreen Harmsworth for technical assistance; to Barbara Bavester and Jean Goodchild, of Edmonton Chest Clinic, for secretarial assistance; and to Mrs. Lawrie Stradling, Edna Lee, and Mrs. F. J. Fraser, of North Middlesex Hospital, and Sandra Johnson, of the Institute of Diseases of the Chest, also for secretarial assistance.

We wish also to record our appreciation to Messrs. Eli Lilly for supplies of penicillin-V potassium (" V Cil K "), and to Messrs. Lederle for supplies of tetracycline (" achromycin "), and to both firms for a grant towards the expenses of the trial. To Messrs. Eli Lilly we express our thanks for their invaluable assistance in the preparation, bottling, and distribution of the capsules in code numbers to the participating chest clinics. It is a particular pleasure to thank all the chest physicians, their staffs and health visitors, the bacteriologists, and general practitioners for their tireless co-operation.

The names of the participating chest physicians are given below, together with the clinics and hospitals at which the investigation was carried out.

Ashford: Dr. P. Baldry, Dr. D. B. Rook. Barrow: Dr. J. R. Edge, Dr. J. C. P. Weber. Birmingham: Yardley Green Hospital, Dr. H. J. T. Ross. Bournemouth: Dr. W. H. Tattershall, Dr. A. T. Hendry. Bristol: Tower Hill, Dr. A. T. M. Roberts, Burton-on-Trent: Outwoods Hospital, Dr. M. B. Paul. Camberwell: Dr. K. Marsh. Camborne: Dr. B. A. Gwynne Jenkins, Dr. E. W. Hughes, Dr. R. L. Ray. Cambridge: Dr. M. J. Greenberg, Dr. R. Bruce. Cardiff: Dr. S. H. Graham, Dr. H. A. Evans. Croydon: Dr. R. H. J. Fanthorpe, Dr. J. F. Heffernan. Doncaster: Dr. F. N. C. Holden. Dudley: Dr. M. Sheldon. Dundee: Dr. R. N. Johnston, Dr. R. T. Ritchie. Ealing: Dr. H. Climie. Edmonton: Dr. R. S. Francis. Epping: Dr. V. U. Lutwyche. Epsom: Dr. S. A. C. Hunter. Farnworth: Dr. J. L. Armour, Dr. F. R. Glover. Finchley: Dr. B. Butterworth. Glasgow: Belvidere Hospital, Dr. R. S. Kennedy; Knightswood Hospital, Dr. G. Johnston; Southern General Hospital, Dr. R. J. Cuthbert. Hammersmith: Dr. Peter Stradling, Dr. D. G. Massey. Ipswich: Dr. Charles Stewart, Dr. P. Embleton, Dr. D. van Zwanenberg. Islington: Dr. J. Wallace Craig. Kingston, Surrey: Dr. S. R. Wilson, Dr. C. O. Edwards. Lewisham: Dr. Mary Farquharson. Leicester: Regent Road, Dr. C. M. Connolly; London Road, Dr. M. C. Brough. Liverpool: N. Liverpool, Dr. W. D. Gray; S. Liverpool, Dr. F. E. Crawley. Mansfield: Ransome Hospital, Dr. D. Davies, Dr. J. J. Glowinski. Merton and Morden: Dr. E. Sanders. Newcastle upon Tyne: Dr. P. O. Leggat, Dr. L. W. Carstairs. Nottingham: Dr. J. V. Whittaker. Oxford: Dr. F. Ridehalgh, Dr. N. J. England, Dr. J. M. Black, Dr. W. S. Hamilton, Dr. D. O. Lewis. Paddington: Dr. J. A. Keeping, Dr. Z. M. Hall. Reading: Dr. A. J. Karlish. Sheffield: Dr. D. H. Anderson, Dr. R. H. Townsend. Southend: Dr. E. G. Sita Lumsden, Dr. J. D. Stevens. Sunderland: Dr. A. B. White, Dr. G. H. N. Bates. Sutton: Dr. H. F. Harwood. Swansea: Dr. T. W. Davies, Dr. G. L. Lewis. Tonbridge: Dr. S. J. Sutton, Dr. R. G. May. Uxbridge: Dr. J. Nicol Roe. Warrington: General Hospital, Dr. R. M. White. Walthamstow: Dr. Hugh Ramsay. Willesden: Dr. C. H. Toussaint, Dr. J. R. Mikhail. Wimbledon: Dr. F. J. H. Walters. Wrexham: Dr. E. Clifford Jones, Dr. J. E. Wilson, Dr. J. F. Durrans, Dr. M. K. Dhole.

The bacteriologists who carried out the sputum examinations are listed below, together with the names of the peripheral laboratories concerned (see text).

Dr. Elizabeth L. Batchelor, Southern General Hospital, Glasgow. Dr. H. R. Cayton, Public Health Laboratory, Bristol. Dr. P. B. Crone, Public Health Laboratory, Sunderland. Dr. J. M. S. Dixon, Public Health Laboratory, Ipswich. Dr. E. H. Gillespie, Public Health Laboratory, Sheffield. Dr. E. G. Gordon, Wordsley Hospital, Worcester. Dr. D. M. Green, Bacteriology Department, University of St. Andrews. Dr. G. J. G. King, Public Health Laboratory, Boscombe. Dr. W. Kwantes, Public Health Laboratory, Swansea. Dr. H. Lederer, Royal Infirmary, Glasgow. Dr. H. Loewenthal, Chase Farm Hospital, Enfield. Dr. N. S. Mair, Public Health Laboratory, Leicester. Dr. G. B. Manning, Royal Infirmary, Bolton. Dr. T. D. M. Martin, Royal Berkshire Hospital, Reading. Dr. A. J. Oliver, Fazakerley Hospital, Liverpool. Dr. R. A. M. Oliver, Mayday Hospital, Thornton Heath. Dr. E. W. Price, Yardley Green Hospital, Birmingham. Dr. H. C. Purdie, Knightswood Hospital, Glasgow. Professor D. T. Robinson, Public Health Laboratory, Liverpool. Dr. J. A. Rycroft, Westcliff Hospital, Southend-on-Sea. Dr. B. J. Stephens, St. David's Hospital, Cardiff. Dr. J. M. Talbot, Kingston Hospital, Kingston-upon-Thames. Dr. M. Thomas, Public Health Laboratory, Edmonton. Dr. J. E. Tinne, Royal Infirmary, Glasgow. Dr. R. L. Vellum, Public Health Laboratory, Oxford. Dr. A. E. Wright, Public Health Laboratory, Newcastle upon Tyne.

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A TRIAL OF PHENETHICILLIN IN CHRONIC BRONCHITIS

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Phenethicillin is the potassium salt of 6-(α-phenoxypropionamido)penicillanic acid. Knudsen and Rolinson (1959) have shown that when given by mouth the serum concentrations are at least twice those obtained with equivalent doses of potassium salt of penicillin V (phenoxymethylpenicillin) and at least equal to those obtained from the intramuscular injection of approximately equivalent weights of the sodium salt of crystalline penicillin G. Garrod (1960) has emphasized that the antibacterial action of these newer penicillins is not identical with that of penicillin G and considers their place to be doubtful apart from staphylococcal infections. The British Tuberculosis Association (1960) report on chemotherapy in chronic bronchitis indicated that penicillin V, 312 mg. twice daily, was as effective as tetracycline, 250 mg. twice daily, in reducing absence from work.

The Investigation

We record here a double blind controlled trial in a group of 40 patients who were selected on standards similar to those used in the British Tuberculosis Association (1960) report. Patients were wage-earning males between the ages of 30 and 65, working at the time, but with a history of bronchitis over the past three years and at least two certified absences from work due to this complaint. The patients selected were considered to be co-operative and likely to persevere with treatment. Excluded from the trial were those with predominant wheezing, those with any pulmonary lesion other than emphysema, and those with a history of heart failure or any other condition likely to affect their working capacity.

Patients were allotted at random to group A, receiving phenethicillin, or group B, receiving a similar placebo tablet containing dicalcium phosphate and sucrose. In addition to clinical assessment, preliminary examination included a postero-anterior radiograph of the chest, a 24-hour collection of sputum in a graduated flask, two morning sputum specimens for laboratory examination, an estimation of the peak flow rate (mean of three readings) using the Wright peak flow meter (Wright and McKerrow, 1959), and the resting and exercise ventilations, using the Wright respirometer. The exercise test was measured when ten steps had been climbed four times at a standard rate of 116 a minute, controlled by a metronome. (" Normal " values for the last three procedures were obtained by carrying out these tests under identical conditions on twenty men of similar age whose chest radiographs were normal and who had no history of previous bronchitis or present respiratory symptoms.) Patients were given a diary in which to record their general condition as " better," " no change," or " worse," and also the colour of the sputum. Each Sunday a

24-hour sputum collection was measured and the volume entered in the diary. The almoner interviewed each patient and recorded days lost from work owing to bronchitis in the preceding three years and verified by the Ministry of Pensions and National Insurance.

Treatment was started on October 17, 1960, and was continued for six months. Each month the patients were seen at a special evening clinic when the following were recorded: clinical progress; any exacerbation of bronchitis (defined as an exacerbation of cough and sputum in which the latter was more purulent); the number of days off work; the grade of dyspnoea (Fletcher, 1952); the peak flow reading; resting ventilation and exercise ventilation tests; present number of cigarettes smoked daily; any toxic effects from the tablets; any omission of the tablets; and whether any chemotherapy had been prescribed by the patient's own doctor. The number of tablets remaining in the bottle was counted and a new bottle issued. The 24-hour specimen of sputum collected the previous day was brought for examination to check the patients' own record in the diary. The almoner interviewed all patients who were away from work. At the final review in April we recorded, in addition, the patient's own assessment of his condition throughout the winter, repeated the postero-anterior radiograph of the chest, and sent a further two morning sputum specimens to the laboratory. No concentration or liquefaction techniques were employed in the examination of the sputum. Antibiotic sensitivities were measured for the principal pathogens.

Results

Four patients were withdrawn from the trial. One in group A was withdrawn because he was unfit for work when the trial began and has remained unemployed throughout, and another, also in group A, because he proved unreliable and failed to attend regularly. In group B a patient failed to co-operate and another ceased taking his tablets because of gastric upset. Mild toxic symptoms were noted in a further three patients —one (group B) had transient nausea and anorexia, one (group A) had occasional vomiting, and another (group A) complained of headaches and reduced the dose to one-half for ten days. On counting the remaining tablets, all, except one to two patients each month, were found to have the correct number remaining. As the numbers of patients are small it is important to test the comparability of the two groups (Table I).

TABLE I.—*Preliminary Assessment*

	Group A	Group B	
Number of patients remaining	18	18	
Average age	55 years	56 years	
Average work days lost per patient in previous winter	33	34	
Cigarettes per day (1 patient in each group reduced)	6 (20→5)	8 (15→5)	
Initial grade of dyspnoea ..	2·2	2·2	
Initial peak flow reading (litres/min.)	193	188	N=447
Initial resting ventilation (l.)	25·28	24·34	N=19·3
,, exercise ,, ,,	18·39 (av. of 15)	18·07 (av. of 14)	N=16·5
,, sputum volume ..	1·25 oz. (35 g.)	1·59 oz. (45 g.)	
Sputum initially mucopurulent	10	10	

The results are shown in Table II. Comparison of the number of days lost from work per patient shows that the observed difference is less than twice the standard error; "t"=1.75; alternatively, P>0.6. No significant difference has therefore been demonstrated. There were no appreciable changes in grade of dyspnoea, or in the peak flow reading, resting ventilation, and exercise ventilation tests during the period of study. The principal pathogens isolated from the sputum initially were *Haemophilus influenzae* in four patients, *Streptococcus pneumoniae* in two, and *Staphylococcus pyogenes* in three; at the end of treatment the respective numbers were one, one, and four. Sensitivity tests showed that the four *H. influenzae* organisms isolated initially were all penicillin-resistant (two in each group), while one of the *Staph. pyogenes* organisms was also penicillin-resistant. Two patients had acquired penicillin-resistant staphylococci by the end of the trial.

TABLE II.—*Results*

	Group A	Group B
Average work days lost per patient ..	19·5	31
Mean days off per 100 exposed to risk	10·7	17
No. of patients never off work (allowing up to 2 days' absence)	8	10
Number of "exacerbations" in each group (>2 days off work)	9	11
Patient's assessment:		
Improved	10	8
No change	4	6
Worse	4	4

Conclusions.—This double blind trial employing phenethicillin, 250 mg. twice daily and a placebo, in a group of 40 patients with moderately severe chronic bronchitis, failed to show any significant benefit from the treatment.

We gratefully acknowledge our indebtedness to Dr. E. T. Knudsen, of Beecham Research Laboratories, for the "broxil" and placebo tablets used in this trial, to Dr. W. A. Wilson, of the department of social medicine, Queen's College, Dundee, for advice on the statistical analysis; and to Nurse E. Stuart, Nurse G. Taylor, Mrs. P. Brough, and Mr. D. Allan for the help they gave.

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The two Middlesex audiology clinics at Heston and Tottenham have been functioning for some time. Any child residing in the county who needs a full investigation of his hearing can be referred to these clinics through the Area Medical Officers concerned. The Tottenham clinic recently moved to a new building which contains a large acoustically treated and air-conditioned room for clinical examination and testing. A new building was planned some time ago for the Heston unit and this is now in course of erection. The centre will have a large room for clinical examination and testing and one for the various audiometric tests (pure tone and speech audiometry), both fully sound-proofed and air-conditioned. There will also be a room for the teacher of the deaf (auditory training), a room for the psychologist (for intelligence testing), and a room for making impressions from ears for hearing-aid inserts. The staff room will also serve as an observation room, with two one-way viewing windows for purposes of instruction. Visitors will be able to observe the clinical examination and testing and the various audiometric tests. It is hoped that the new unit, which will be called the Hearing Centre, will be completed in six months' time.

GENERAL ANAESTHESIA FOR TRACHEOSTOMY IN ACUTE LARYNGEAL OBSTRUCTION IN CHILDREN

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The commonest forms of acute inflammatory laryngeal obstruction in childhood are acute laryngitis and acute laryngo-tracheo-bronchitis. Both infections are of remarkably sudden onset, though there may be a history of an insignificant infection of the upper respiratory tract. In both conditions there is rapidly increasing respiratory embarrassment, with inspiratory stridor, a harsh irritating cough, a hoarse muffled cry, intercostal recession, cyanosis, and a very considerable fear and distress. Signs of increasing obstruction are a rising pulse rate and restlessness.

In acute laryngitis the epiglottis and the subglottic region are particularly inflamed and swollen, because in these areas the submucosa is lax. Acute epiglottitis has been described as a separate entity. In such cases, once the obstruction has been bypassed by tracheostomy, recovery should be uneventful. It is often possible to remove the tube within three days.

In acute laryngo-tracheo-bronchitis the inflammation of the larynx may not be so severe, but an inflammatory oedema with exudation affects the whole lower respiratory tract. The problem here is to provide for the removal of somewhat viscid secretions in a child with a cough that is inefficient because of laryngeal inflammation. Tracheostomy not only affords a way of bypassing the inflamed larynx but also allows for aspiration of the secretions from trachea and bronchi and reduction of dead space. Recovery is not usually as rapid as in the first group. It may be a week or more before the tracheostomy tube can be removed.

Choice of Anaesthesia or Analgesia

When the decision has been made that tracheostomy is necessary it can be performed under local analgesia or general anaesthesia.

At the end of the nineteenth century anaesthesia by chloroform was used for tracheostomy in children suffering from diphtheria (Beaupère, 1888; Broca and Hartmann, 1887; Weiss, 1888), but a number of fatalities were reported, often due to fatal respiratory obstruction developing before tracheostomy could be performed. General anaesthesia in these circumstances acquired an evil reputation, and the use of local analgesia became customary.

A review of the literature suggests that this prejudice in favour of local analgesia is still widespread (Neffson, 1942; Briggs and Heseltine, 1952; Leegaard and Lindeman, 1954; Nelson, 1958; Forbes, 1961). Operative conditions under local analgesia alone, especially in infants, are often unsatisfactory because of struggling and congestion. The value of using general anaesthesia for tracheostomy with an airway assured by preliminary bronchoscopy or intubation was emphasized by Ibsen (1954). His experience was with patients suffering from poliomyelitis. Davenport and Rosales (1959) recommend intubation followed by general anaesthesia.

Bryce-Smith (1957) has pointed out that improvement of the airway before tracheostomy allows the operation to be carried out peacefully and without undue venous congestion. An emergency operation is relieved of several hazards and the complications are reduced to those of elective tracheostomy. Booth, Nisbet, and Wilson (1960), in discussing the practical problems encountered in anaesthesia for paediatric surgical emergencies, endorsed the value of general anaesthesia for tracheostomy, especially in infants. They recommended an apnoeic technique using intravenous thiopentone, suxamethonium, and intubation, preceded by five minutes' oxygen given through a face-mask. In cases where intubation was likely to be difficult a non-apnoeic technique was used.

Clinical Experience

In the Amersham General Hospital and associated hospitals, over the 10 years 1951–60, 57 patients with acute laryngitis or laryngo-tracheo-bronchitis were treated, eight of them under 2 years of age. Tracheostomy was performed in 17 of these cases (see Table). In six cases local analgesia was used and two of these patients subsequently died. In the remaining 11 cases a general anaesthetic was given for the tracheostomy.

Details of Cases

Age in years:	<1	1	2	3–5	>5	Total
No. of cases:	2	6	2	5	2	17
Tracheostomy under local analgesia	1 (died)	3 (1 died)	1		1	6
Tracheostomy under general anaesthesia	1	3	1	5	1	11
Year:						
1951					1	1 (L.A.)
1952	1					1 (L.A.)
1953		1	2			3 (2 L.A., 1 G.A.)
1954	1					1 (G.A.)
1955						
1956						
1957				1		1 (G.A.)
1958					1	1 (G.A.)
1959		3				3 (2 L.A., 1 G.A.)
1960		2		4		6 (G.A.)

All cases occurred between October and February with the exception of a child of 2 years suffering from acute epiglottitis in August. Most of the children in this series were admitted to the children's ward under the paediatrician. They were seen as soon as possible after admission by an E.N.T. surgeon and the decision was made whether immediate tracheostomy was necessary or not.

General anaesthesia was used at the suggestion of the paediatrician, Dr. D. MacCarthy, who was appalled at the terror and struggling which can occur when a tracheostomy is performed for this condition in a small child under local analgesia. The child is seriously ill and usually distressed. Some patients have a degree of heart failure, as the right side of the heart is working against raised pulmonary capillary resistance due to the high alveolar pressure created by the forced expiration which follows each inspiratory effort. The violent struggling which is apt to occur when tracheostomy is performed under local analgesia may precipitate cardiac failure.

General anaesthesia can usually be induced without a struggle, and in all the cases in this series an endo-

tracheal tube was passed under direct vision. The resulting motionless oxygenated patient, with reduced venous congestion, enables the surgeon to perform the tracheostomy deliberately at the site of election and to obtain haemostasis.

Method of General Anaesthesia

It cannot be overemphasized that in any surgical procedure involving the airways there must be complete understanding between surgeon and anaesthetist. They must know exactly what they will do in every eventuality. In each case anaesthesia was induced with the surgeon scrubbed up and standing beside the patient, ready to perform tracheostomy as an emergency procedure if required. In this series of cases it has not been necessary.

All cases except the last two were given premedication with atropine in the following dosage: aged 3–12 months, 0.4 mg. (1/150 gr.); over 1 year, 0.6 mg. (1/100 gr.). In the last two the atropine was omitted deliberately because of marked tachycardia. No embarrassment resulted from the omission.

Induction of anaesthesia was in each case by inhalation; in one case oxygen, cyclopropane, and ether were used; in two cases oxygen, halothane, and ether; and in the rest oxygen, ethyl chloride, and ether. Oral intubation was performed under direct vision in all cases, and anaesthesia was maintained with nitrous oxide, oxygen, and ether.

Discussion

Choice of Anaesthesia

The danger of inducing general anaesthesia in a patient with partial respiratory obstruction due to inflammatory glottic oedema has been described by Macintosh (1949). It has become an accepted principle in anaesthetic teaching that in such cases the airway is secured (usually by blind nasal intubation helped by topical analgesia) prior to the induction of general anaesthesia. This method is impracticable in small children with laryngo-tracheo-bronchitis.

The induction of anaesthesia in these cases without first securing the airway involves the risk that the partial respiratory obstruction may become complete before tracheostomy can be performed. This calculated risk is considered worth while. General anaesthesia before tracheostomy offers advantages to both patient and surgeon. First, the patient avoids the psychological trauma of an operation which must be terrifying to a child under local analgesia. Secondly, in the absence of struggling under general anaesthesia, no further load is placed on an embarrassed circulation.

The cardiac reserve in these patients is lowered if the respiratory obstruction has been prolonged. Respiration is usually rapid and shallow, ventilation is inadequate, and the effective tidal volume is reduced towards the volume of the dead space, causing anoxia and retention of carbon dioxide in spite of forced expiration. The alveolar expiratory gas pressure is greatly raised and the negative pressure developed in inspiration is increased. This in turn causes pulmonary congestion and oedema, and the right side of the heart has to work against a raised pulmonary capillary resistance. The increased expiratory alveolar pressure causes generalized venous congestion and lowered venous return to the heart and thus a lowered cardiac output.

Under these conditions prolonged struggling could prove fatal. The induction of general anaesthesia can usually be achieved smoothly and without struggling. Restoration of the airway on intubation relieves the anoxia, reduces dead space, and reverses the chain of events which has led to the deterioration of the pulmonary circulation.

The surgeon operates on a still, adequately oxygenated patient; he can carry out a planned instead of an emergency tracheostomy and he does not have to combat the excessive bleeding associated with engorgement of the neck veins. Relief of the respiratory obstruction before operation diminishes the risk of mediastinal emphysema and pneumothorax.

In this series the impression has been gained that the post-operative condition and subsequent progress of children who have had general anaesthesia for the tracheostomy has been most satisfactory. It is not reasonable to draw a sharper comparison between the results of the local and general anaesthetic cases in this series. This decade brought great advances in the management of patients with tracheostomy and in antibiotics. The mortality from the disease is steadily falling.

Technique

Induction by inhalation has been preferred because intubation can sometimes be very difficult. The inflammation and oedema may produce asymmetrical distortion of the anatomy, and a direct view of the cords may be impossible. The use of a relaxant drug makes intubation easy, but in these cases one often needs more time than in a normal child and a long period of apnoea could be fatal.

All the agents used provided a smooth rapid induction for ether anaesthesia, which was maintained at a light level. It will be generally agreed that these are not cases for the occasional or inexperienced anaesthetist.

Summary

A series is reported of 57 cases of acute inflammatory laryngeal obstruction in children. Tracheostomy was performed in 17. General anaesthesia was used in 11 cases and local analgesia in 6. There were two deaths, each after tracheostomy under local analgesia.

The relative merits of general anaesthesia and local analgesia for the tracheostomy are discussed.

A preference for general anaesthesia is expressed.

We thank Dr. Dermod MacCarthy for permission to publish this series of cases admitted under his care, and for his encouragement and inspiration; Miss Esme Hadfield for her advice and help in the preparation of this article; and Dr. Jean Clark for assistance in providing the figures.

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TREATMENT OF EXPERIMENTALLY INDUCED BRONCHOSPASM BY AIR-AND-OXYGEN MASSAGE OF THE LUNGS

BY

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Total bronchospasm sometimes occurs during thoracic operations and is a complication which anaesthetists dread. It is also seen in bronchial asthma and as a result of poisoning by certain chemical agents (Ariev, 1952; Buyanov, Riabov, and Smirenskaya, 1959). There is a dearth of literature on bronchospasm and effective methods of its treatment. As a rule it is treated by anticholinergic and sympathomimetic agents, but these drugs are often either of little use or totally ineffective.

At the Institute of Thoracic Surgery, Moscow, total bronchospasm that had developed in a patient suffering from mitral stenosis was effectively treated by direct massage of the lung. This confirmed the hypothesis advanced by Smolnikoff that total bronchospasm may be regarded as a form of pulmonary arrest which is similar to cardiac arrest and which therefore can be treated by direct massage. We decided, however, to look for less traumatic means of massaging the lungs.

In the medical literature at our disposal we were unable to find any reference to lung massage for bronchospasm, and so we designed a very simple apparatus (Figs. 1 and 2) with which several cases of experimentally induced bronchospasm in dogs have been successfully treated.

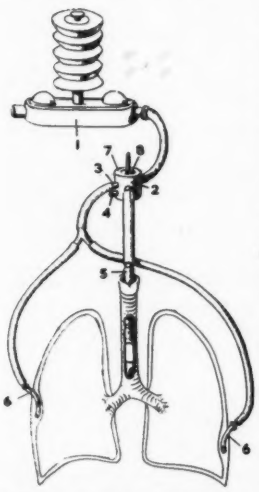

FIG. 1.—Diagram of the lung-massage machine. (1) Air pump. (2) Metal three-way cock. (3) Inspiratory tubes. (4) Expiratory tubes. (5) Endotracheal tube. (6) Curved cannulas. (7) Body of the three-way cock. (8) Three-way cock piston.

The apparatus consists of two parts—a pump and a three-way cock. The pump consists of Oxford bellows (1) which serve to inflate alternately the pleural cavities and the lungs, and a system of rubber tubes which deliver either air or an air–oxygen mixture. The three-way cock (2) serves to direct the flow of gases first into the lungs during inspiration and then into the pleural cavities during expiration. The cock consists of a metal body with a movable valve (8) which has a specially bored canal. One rubber tube connects the bellows to the three-way cock, and two other tubes lead away from it. One of them is connected to the endotracheal tube, the other to two tubes each bearing a curved cannula. These serve to "intubate" the pleural cavities. This apparatus creates passive inspiration and expiration. When the three-way cock connects tube "a" with tube "b" the pumped air is directed into the lungs. Air which is found in the pleural cavities will be displaced by the expanding lungs and will be forced outside, through the curved cannulas, into the tubes (6). When tube "a" is connected with tube "c" the pumped air will be directed into the pleural cavities. This results in collapse of the lungs, and the air is displaced from the lungs outwards via tube "b."

Thus by alternating the position of the valve it is possible to obtain passive inspiration and expiration.

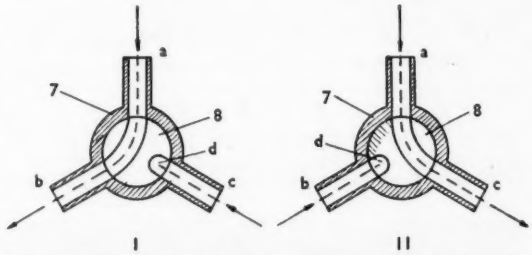

FIG. 2.—Transverse section of the three-way cock. Position I: (7) body; (8) piston. Channel a–b: position of the piston during inspiration. Position II: piston's position during expiration, when the air is pumped into the pleural cavities.

Method

Experiments were made on nine dogs weighing between 15 and 35 kg. Premedication, which was given to the animal 30 to 40 minutes prior to the experiment, consisted of a subcutaneous injection of a 1% solution of "omnopon" (3 mg./kg. body weight). The dog was then placed on the operating table and its right or left femoral artery and vein were denuded. The artery was cannulated for continuous recording of arterial pressure. Initial data such as respiration rate, pulse, arterial pressure, electrocardiogram, and electroencephalogram were then recorded.

The induction with an 0.8% solution of thialbarbitone ("khemital") was followed by intubation. Spontaneous breathing was preserved. An intratracheal spirogram was recorded (see (*a*) in Fig. 3). The skin was then painted at the sides of the chest wall in the seventh interspace on the right and in the eighth interspace on the left (owing to the proximity of the heart), along the axillary line. An incision of 0.5 cm. was made and curved cannulas (diameter 3–4 mm., length 5 cm.) were inserted.

Intrapleural spirograms and variations of intrapleural pressure were continuously recorded (see (*b*) in Fig. 3). Then 0.05% neostigmine, 0.3–0.6 mg./kg. of body weight, was injected (average 9–18 mg.). Bronchograms were taken at the height of the bronchospasm, and in some cases pieces of lung tissue were taken for biopsy. In three experiments the usual doses of neostigmine were found inadequate to produce bronchospasm and an extra 3 to 13 mg. was added.

After two to five minutes of bronchospasm air-and-oxygen massage of the lungs was started. A bronchogram was taken and was repeated 5 to 10 minutes after the removal of the bronchospasm. As spontaneous respiration returned, the respiratory rate and pulse were recorded and pieces of lung tissue were again taken for histological examination.

In order to register all the above data we connected the endotracheal tube and the intrapleural cannulas with a Marey capsule and a mercury manometer.

Results of the Experiments

We carried out 11 experiments on nine dogs. Our data show that with an initial respiratory rate of 11–13 a minute, an intratracheal pressure of 3–4 mm. Hg, and an intrapleural pressure of 7–8 mm. Hg neostigmine-induced bronchospasm developed at variable intervals of time from 30 seconds to 4 minutes (Fig. 3, I).

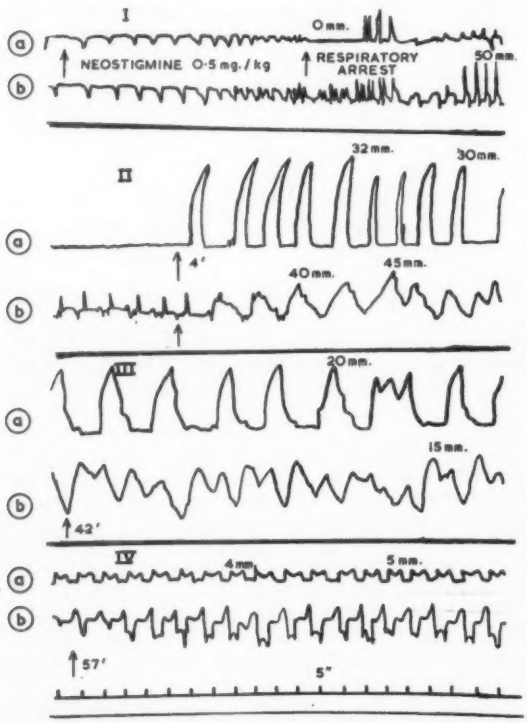

FIG. 3.—Spirograms of spontaneous breathing and of the beginning of the bronchospasm. Kymograms were recorded in the following order from above below: (*a*) record of respiration; (*b*) record of intrapleural pressure. (I) Spontaneous respiration, the beginning of bronchospasm, and the respiratory arrest. (II) Air–oxygen massage of the lungs four minutes after respiratory arrest. (III) Air–oxygen massage of the lungs 42 minutes after respiratory arrest. (IV) Resumption of spontaneous respiration after 57 minutes.

Respiration stopped entirely and the intratracheal spirograms became a straight line. There were single vibrations and changes of pressure which were probably due to fibrillation of the intercostal muscles, the diaphragm, etc. They sometimes lasted three to four minutes. When they appeared the intrapleural pressure rose sharply (up to 40–50 mm. Hg) and vibration frequency reached 17–19 a minute. Similar changes, which apparently had the same aetiology, were recorded in the trachea. Later on the intratracheal pressure did not change from the straight line (Fig. 3, II). The number of vibrations inside the pleural cavities perceptibly decreased—up to 6–11 a minute—and the pressure fell to 30–35 mm. Hg.

We started lung massage two to five minutes after the development of the bronchospasm. With the aid of the Oxford bellows we produced 7–10 passive inspirations and expirations. Intratracheal pressure varied between 30 and 32 mm. Hg and the intrapleural pressure between 40 and 45 mm. Hg (Fig. 3, II). Some 8 to 10 minutes after the massage had been started we noticed that the pressures inside the trachea and the pleural cavities were equal. This equalization of pressures may have been due to decrease of resistance to expiration—that is, to partial decrease of the bronchospasm.

In some instances we experimented with double or triple inspirations followed immediately by double or triple expirations (Fig. 3, III). This manœuvre was accompanied as a rule by a rise of the intratracheal pressure. Towards the end of the massage both the intrapleural and the intratracheal pressures decreased to 10 mm. Hg.

Spirograms of spontaneous respiration after lung massage showed that pressure in the pleural cavities exceeded that in the trachea. The maximum for intrapleural pressure was 20–35 mm. Hg and that for intratracheal pressure 15–18 mm. Hg. These results confirmed the data obtained with the aid of bronchography. Bronchograms were taken at the height of the bronchospasm, and also 5 and 10 minutes after the massage had begun. To take a bronchogram the head of the table was raised to an angle of 50 degrees. The opaque dye was injected into a No. 12 endotracheal tube with the aid of Janet's syringe (30–40 ml. of a 40% solution of lipiodol).

Bronchograms taken at the height of the bronchospasm (Fig. 4, A) indicated that the opaque dye filled the trachea, the right and the left bronchus, and their major ramifications—the segmental bronchi. The smaller bronchi and the alveoli usually remained free from the dye. Five minutes after the air massage of the lungs (Fig. 4, B) the penetration of the dye into the bronchioles and the alveoli was clearly visible. Some lipiodol remained in the larger bronchi. Ten minutes after massage (Fig. 4, C) the dye was in the alveoli. After about 40–64 minutes of massage, when the bronchospasm had been removed and spontaneous respiration established, the structure of the bronchial tree assumed the same appearance as in the initial bronchogram. If no massage was done the lumen of the bronchi was progressively reduced until death occurred.

Data on Additional Investigations

We have seen that with bronchospasm at its height the arterial blood-pressure rose from 130–140 to 170–180 mm. Hg. On starting massage of the lung the arterial blood-pressure fell rapidly and reached 60–70 mm. Hg. Then as the massage proceeded the blood-pressure rose gradually and had returned to its initial level by the time spontaneous breathing restarted.

After the injection of neostigmine the pulse slowed down from 120–130 to 70–75 a minute. With bronchospasm at its height a bradycardia of 40–45 a minute developed. Air massage of the lung increased the pulse rate to 90–100 a minute. This rate was maintained with the return of spontaneous respiration.

Some 40–60 seconds after the injection of neostigmine we observed nodal rhythm on the E.C.G. in the majority of instances. At the height of the bronchospasm this rhythm was transformed into a complete atrioventricular block. The air massage of the lung led to the re-establishment of sinus rhythm after 10–15 minutes in two cases, and after 20–25 minutes in five cases (E.C.G.s were not taken in three cases). When spontaneous respiration returned the E.C.G. resumed its initial configuration.

Investigation of the electrical activity of the brain showed that 10–19 seconds after the injection of neostigmine slow waves appeared with a certain increase of amplitude in the sensory and motor areas. With return of spontaneous respiration the E.E.G. reverted to normal.

The presence of the bronchospasm in our experiments was further confirmed by histological study of lung tissue. Lung biopsy taken at the height of the bronchospasm showed marked narrowing of the lumen of the large and the smaller bronchi, which had a festooned appearance with slit-like lumen, and contained mucus with leucocytes and epithelial cells. Atelectatic areas alternated with areas of gross dilatation (Fig. 5).

In one case we left the animals without the benefit of lung massage in order to study the clinical picture of bronchospasm in its natural state and the death of an animal which had received a lethal dose of neostigmine.

The presence of bronchospasm was confirmed by the histological examination of biopsy material taken at the height of the attack. In lung tissue examined one hour after clinical death there was no histological evidence of bronchospasm (Fig. 6). The bronchial lumen was wide open and the absence of the spasm in this case was probably explained by the development of post-mortem relaxation.

Summary

Total bronchospasm in anaesthetized dogs was induced with adequate doses of neostigmine.

With the aid of our apparatus for air-and-oxygen massage of the lungs it was possible to remove the bronchospasm and re-establish spontaneous breathing without resorting to thoracotomy.

All changes in the cardiovascular system and in the electroencephalographic pattern caused by the bronchospasm were gradually modified by massage of the lungs.

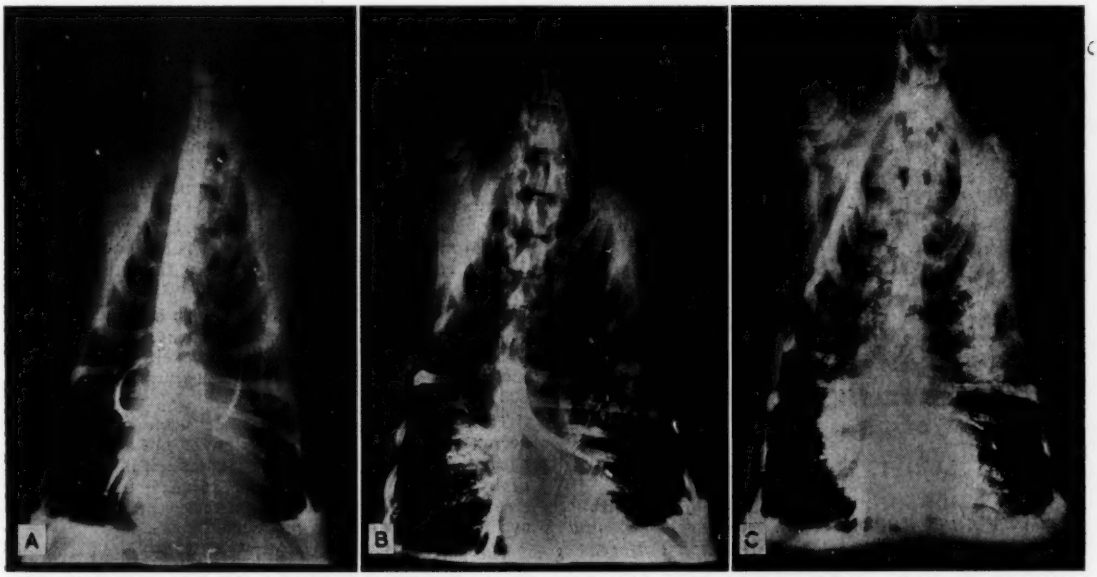

Fig. 4.—Removal of neostigmine-induced bronchospasm by air massage. A, neostigmine bronchospasm. Opaque dye injected at height of bronchospasm fills only the trachea and main bronchi. B, bronchogram five minutes after air massage of the lungs. The dye has penetrated into the smaller bronchi and the alveoli. C, bronchogram 10 minutes after air massage of the lungs. The bronchospasm has been removed; the dye is in the alveoli.

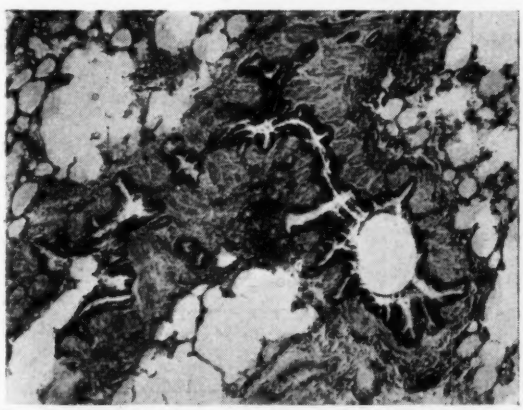

Fig. 5.—Photomicrograph of lung tissue. The smaller bronchi have a festooned appearance with slit-like lumen, filled with mucus.

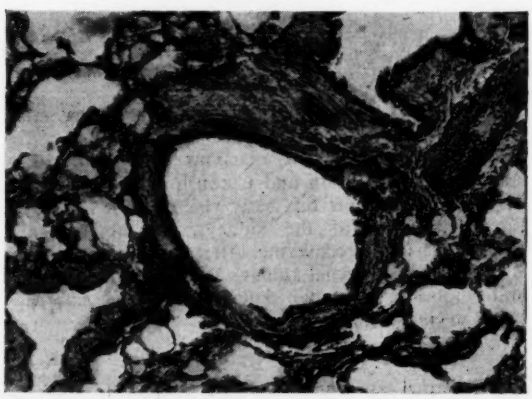

Fig. 6.—Photomicrograph of lung tissue. Bronchi after death. There is no evidence of spasm. The bronchial lumen is wide open.

These changes reverted to normal as spontaneous respiration was re-established.

The method of lung massage suggested is less traumatic and more effective than the direct method suggested by Smolnikoff. When the aetiology of the bronchospasm is unknown or when the spasmolytic drugs are ineffective lung massage by our method may prove to be a life-saving measure.

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REVERSIBLE ACUTE RENAL TUBULAR NECROSIS DUE TO ANTI-Le^a

SUCCESSFUL TREATMENT BY HAEMODIALYSIS

BY

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Since the discovery of the Lewis blood-group system by Mourant in 1946 there have been at least 10 reported instances of transfusion reactions due to anti-Le^a. According to Mollison and Cutbush (1955) these may be mild. We report one case which resulted in acute tubular necrosis of the kidneys, the uraemic and comatose patient recovering after haemodialysis on a Kolff twin-coil artificial kidney. We discuss the serology and emphasize again the dangers of using unmatched blood in transfusions.

Case Report

A married woman aged 20 reported transient intermenstrual vaginal bleeding one week before she was admitted to hospital complaining of pain in the lower abdomen with vomiting and further minimal vaginal bleeding. Physical examination showed no signs of peritoneal irritation, her blood-pressure and pulse were quite normal, and a diagnosis of threatened abortion was made.

Next day she collapsed quite suddenly with severe abdominal pain; a laparotomy was performed and a ruptured right tubal ectopic pregnancy excised. In this episode her systolic blood-pressure remained at a level of 70 mm. Hg for a period of three hours. She was given 5 pints (2.8 litres) of group O Rh-negative blood which was not cross-matched. After transfusion her systolic blood-pressure rose rapidly to 120 and was maintained. Her general condition was good, and some 400 ml. of urine was removed by catheter. However, on the following day she produced only 180 ml. of urine and on the next day only 60 ml., which was noticeably dark in colour. This degree of oliguria persisted for a further four days. Her only intake was 10% glucose in water by mouth, with 250 mg. of tetracycline q.i.d., on a fluid-balance regime. During the final four days her blood N.P.N. rose from 156 to 238 mg./100 ml. Latterly, persistent vomiting occurred, and she was transferred to our hospital.

On admission seven days post-operatively she was semi-comatose, and was vomiting and screaming irrationally and intermittently. On examination she had facial oedema, generalized twitching, and a blood-pressure of 120/80, and was afebrile; the abdomen showed no special features. The serum ionogram showed serum sodium of 134.5 mEq/l., potassium 6.3 mEq/l., bicarbonate 17.9 mEq/l., and chloride 79.6 mEq/l.; this inferred an abnormally high degree of retention of sulphates, phosphates, or similar anions. Haemoglobin was 12 g./100 ml., and the blood counts showed nothing of note. The blood N.P.N. was 229 mg./100 ml. and creatinine 19 mg./100 ml.; the serum bilirubin was not elevated.

Catheterization provided too small an amount of cloudy yellow acid urine for specific-gravity determination; occasional polymorphs and red cells were present microscopically, and the urine urea concentration was only 800 mg./100 ml.

The clinical impression was of acute renal tubular necrosis, secondary to hypotension at operation or to a haemolytic transfusion reaction. It was felt that the degree of hypotension was possibly not adequate to explain the renal shut-down, and a serological review of blood samples and previous donors was requested.

The patient's coma deepened and she became practically unresponsive to pain stimuli. She was therefore dialysed on a Kolff twin-coil artificial kidney for five hours at an

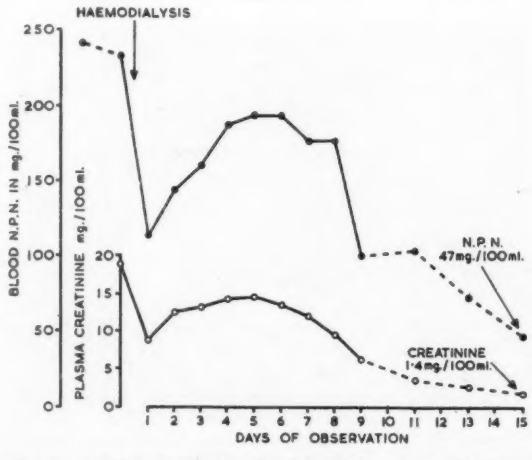

FIG. 1.—Anti-Le^a transfusion reaction with acute renal failure.

average flow rate of 200 ml. a minute. There was an initial period of hypertension, easily controlled by pentolinium tartrate. At the end of the first hour and a half the puffiness in her eyelids had decreased, and shortly afterwards the hiccups disappeared. Her level of consciousness steadily improved until the end of the run. When awaking she was very confused and agitated, and required amylobarbitone sodium 4 gr. (0.26 g.) per rectum.

Chemical effectiveness of the double-coil artificial kidney is recorded in the form of a graph (see Fig. 1). It produced a precipitous fall in N.P.N. and creatinine followed by a steady rise for three days, but not to the original high levels. Thereafter, these levels returned to normal ranges. They may be regarded as indicators of the degree of retention of sulphates, phosphates, or the unknown toxic products which cause clinical uraemia. The secondary rise is common after a fall due to haemodialysis. It presumably represents the shift of retention products from the extravascular space.

The patient rapidly improved over the next few days and was mentally clear on the day after dialysis. She did not relapse clinically, was ambulatory after two weeks, and was then discharged home to Toronto. The urine volume did not reach a normal level until three days after dialysis, but progressed to a marked polyuria by the sixth day, thereafter dropping gradually to a normal daily volume. From Fig. 2

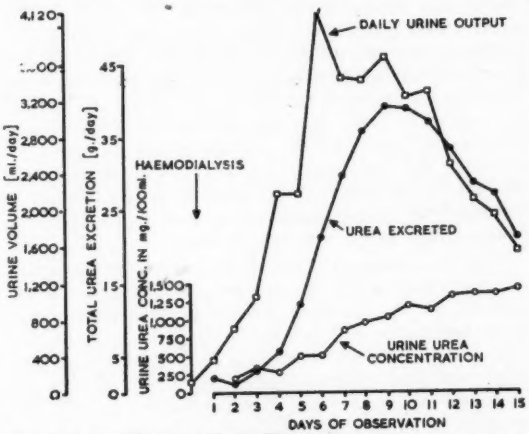

FIG. 2.—Renal function after dialysis on Kolff twin-coil artificial kidney.

it will be seen that while the urea excretion closely paralleled the urine output the ability of the kidneys to concentrate urea rose much more slowly during the whole period of observation. Before discharge the urine urea reached a concentration of 1.5 g./100 ml. The patient has remained well and free from any signs of renal failure over the ensuing two years. We have no information on her degree of return to full renal-concentration function.

Generally in such cases haemodialysis should be carried out when the following biochemical levels are exceeded: blood urea 300–400 mg./100 ml.,* serum potassium 7 mEq/l., a creatinine level of 15 mg./100 ml., and serum bicarbonate falling below 12 mEq/l. (Kolff, 1955). The clinical supervention of coma was really the factor which decided us to carry out the dialysis.

Serology

The results of blood-grouping tests on the patient were as follows: O MNS P DcE/DCe K− Le(a−) Fy(a+). In the saliva, H substance but no Le^a substance was secreted. The direct Coombs test on the sixth post-transfusion day was weakly positive. Anti-Le^a was present in the serum (P=1/1,001). The titre at 20° C. was 1/4. At 37° C. trypsinized and ficinized Le(a+) cells were haemolysed at a titre of 1/8. The indirect antiglobulin titre was 1/16 on a 48-hour specimen to which complement had not been added. In addition to the effects of the anti-Le^a, some other weak activity could be detected at 4° C., which was attributed to the presence of anti-Le^b.

The donors of the unmatched blood were recalled: four were Le(a−) and only one was Le(a+), with red cells incompatible with the serum of the patient. Since there is no history of transfusions or injections of blood, the anti-Le^a in her serum is presumably of "natural occurrence"; about 5% of Le(a−b−) people possess anti-Le^a in their serum (Mollison, 1959a). Mollison (1959b) pointed out that the complement-binding antibodies such as anti-Le^a bring about quite rapid destruction of incompatible donor cells; if their haemolytic properties are pronounced they may even cause intravascular lysis. Most of the reported cases of reactions due to anti-Le^a have been haemolytic in nature (Mourant, 1946; Krieger and Simmons, 1949; DeVries and Smitskamp, 1951; Brendemoen and Aas, 1952; Lauer *et al.*, 1954; Mollison and Cutbush, 1955; Matson *et al.*, 1955; Peterson and Chisholm, 1958; Merrild-Hansen and Munk-Anderson, 1957; Mouliner, 1959), and the present case emphasizes the danger of potent examples of this antibody.

Discussion

The commonest hazard of unmatched group O blood is the presence in it of incomplete anti-A with haemolytic properties. Although this threat can be largely eliminated by the use of suitable tests in the blood bank, some of the donor antigens will invariably be different from those of the recipient, and may be attacked by the products of previous incompatible transfusions, or pregnancies. When the patient has never been transfused or been pregnant, such incompatible donor antigens may either cause a delayed antibody response that is not immediately harmful or, as in this case, encounter a potent antibody of "natural occurrence."

Although only about 0.3% of randomly selected people (Kissmeyer-Nielsen *et al.*, 1955) have such a form of anti-Le^a, and only about one in five random donations will be incompatible, nevertheless such a small risk may have decidedly severe effects when it is least expected.

Summary

An instance of uraemic coma due to acute renal tubular necrosis occurring after an anti-Le^a transfusion reaction is reported in a patient without a history of previous transfusions or injections of blood. The anti-Le^a demonstrated in the patient's serum is presumably of "natural occurrence." Recovery occurred after haemodialysis on a Kolff twin-coil artificial kidney.

The dangers of using unmatched blood for transfusion are again stressed.

We are grateful to Dr. Eric Nation, Director, Red Cross Blood Transfusion Service, Calgary, Alberta, for matched blood used during dialysis.

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*To convert to blood urea nitrogen divide by 2.14.

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SIMPLE TEST-PAPER METHOD FOR THE CLINICAL DETERMINATION OF PLASMA PSEUDOCHOLINESTERASE

BY

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Pseudocholinesterase (ChE) is produced in the liver and is normally present in the plasma, though its precise function is unknown. A simple method for the estimation of this enzyme, requiring no elaborate apparatus, would have certain practical advantages. The ChE level of the plasma falls in certain diseases of the liver and has been advocated as a measure of the damage to this organ; it is also of importance in the control of anticholinesterase therapy in myasthenia gravis. It is, however, in connexion with the use of short-acting muscle relaxants such as suxamethonium, which are normally destroyed *in vivo* by ChE, that a knowledge of the enzyme activity of the plasma is particularly desirable. A small proportion of the population, who are otherwise in good health, are deficient in plasma ChE, and if suxamethonium is used on these patients the time of paralysis may be greatly prolonged. This situation may also arise in patients with severe liver damage undergoing general anaesthesia. Preliminary estimation of the plasma ChE in such subjects would reveal this defect.

Methods for the estimation of ChE are based on the amount of acetic acid liberated from acetylcholine either by causing it to release carbon dioxide from a bicarbonate buffer, as in the manometric technique of Ammon (1933), or by observing the fall in *p*H of a barbitone/phosphate buffered system in a given time (Michel, 1949; Aldridge and Davies, 1952). These methods are accurate but require special apparatus and are laborious and unsuited to clinical work.

More recently, simpler methods based on the colour change of suitable indicators have been published (Caraway, 1956; Rappaport *et al.*, 1959; Smith *et al.*, 1959). Limperos and Ranta (1953) described a method using bromothymol blue in which visual inspection of the mixture of blood and reagents after a short incubation gave an approximate value for the ChE. Herzfeld and Stumpf (1955) described a further simplification of this technique in which filter paper impregnated with a choline ester and bromothymol blue is used. The paper is applied to the plasma or serum to be tested and the time required for the colour of the indicator to change to that of a standard tint, corresponding to the liberation of a definite amount of acetic acid, is a measure of the ChE activity. These test-papers are now commercially available, and we have compared the results given by them with those obtained by the method of Michel (1949).

Material and Method

The subjects were mostly patients undergoing general anaesthesia. In some patients blood was drawn before and after injection of 2.5 or 5 mg. of the anticholinesterase drug neostigmine methylsulphate; in this way widely differing ChE levels were obtained. Samples from a few patients with jaundice were also included.

The test-papers are yellow strips, 4 by 1 cm., which, when cut in half, provide two pieces 2 cm. long and sufficient for two estimations. Exactly 0.05 ml. of serum or plasma from heparinized blood, free from red cells and haemolysis, is placed at the centre of a perfectly clean microscope slide—that is, one that is free from acid or alkali. The test-paper is applied to the drop of serum so that this is completely absorbed. (N.B. The serum must not be applied to the paper.) The colour of the paper then changes to a dark bluish green. At the same time a stopwatch is started. The test-paper is covered with another clean slide, using gentle pressure and taking care to avoid the inclusion of air bubbles between the slide and paper and to secure even distribution of the fluid. As the action of the ChE proceeds the colour of the paper changes through yellowish green tones to the original yellow. When it matches the colour standard supplied with the test-papers (olive green) the time is noted.

The time between contact of the paper with the serum and matching with the colour standard is inversely proportional to the ChE activity of the serum: thus if the time taken is less than 12 minutes a high plasma ChE level is present, whereas if it is 12 to 20 minutes a normal level exists. Times of 20 to 35 minutes or longer denote a low ChE activity. In practice, observation of the test-paper at 12, 20, and 35 minutes is sufficient to identify the grade of ChE activity.* It is recommended that the strip of standard colour should also be included between two slides. Observations should be carried out in a constant light and at average room temperature (20° C.). Serum or plasma may be kept for a day or two in the refrigerator before estimation and the papers must be protected from moisture, ammonia and the fingers.

Results

There was good agreement between the results obtained with the test-papers and those obtained with Michel's method, except at very low levels (see Chart). The initial ChE values of those subjects who received neostigmine were normal by both methods.

Herzfeld and Stumpf (1955) made a comparison of their method with that of Ammon (1933). They did not claim great accuracy for the filter-paper technique (they were using test-papers prepared in their laboratory) but thought it suitable for routine work: we are in agreement with this. They observed that strongly icteric sera gave results somewhat higher than the true value, presumably because the bilirubin alters the tint of the

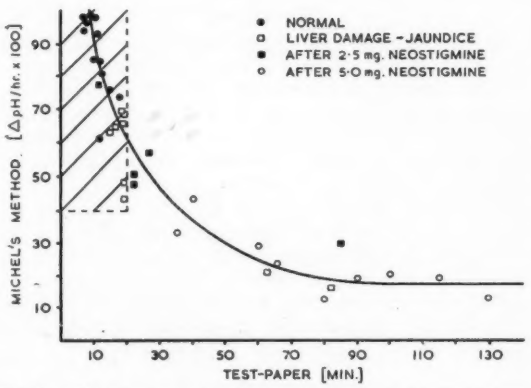
*In more recent batches of test-paper these figures have been slightly modified, 7 to 18 minutes being given as normal; the reaction should then be inspected at 5, 18, and 35 minutes.

bromothymol blue. We have confirmed this effect, which is small and most apparent at low levels of ChE, but it does not detract from the practical value of the test.

A disadvantage of the method is that the colour of the end-point (an olive green) is difficult to identify with precision, and in the case of low values the time at which matching with the standard tint occurs cannot be determined to within 5 or even 10 minutes; for clinical work this is not a serious drawback. The effect of variations of room temperature is small.

The test-paper method has the advantage that the plasma is undiluted, therefore if reversible inhibitors are present their effect is not diminished, as compared with *in vivo* conditions, as would be the case if the plasma were diluted as in other methods.

Ideally the ChE level of every patient receiving an injection of the short-acting muscle relaxant suxamethonium should be tested before the induction of anaesthesia. As the incidence of a low enzyme activity is only about 1 in 2,000 normal patients such a procedure would be impracticable. A familial incidence of this condition has also been noted (Lehmann and Ryan, 1956). Nevertheless, in the presence of liver disease and nutritional deficiencies (such as carcinoma of the oesophagus) a prolonged reaction to the relaxant occurs much more often; it is in such cases that the test will be found of greatest value.



Results with test-paper and with Michel's method. Normal values should fall within hatched area.

Summary

The test-paper offers a simple method for the estimation of plasma pseudocholinesterase, in which the plasma is allowed to act upon a substrate containing acetylcholine and bromothymol blue. The results with this method are in reasonably good agreement with those obtained from Michel's method, and although it is not a method of great precision it is suitable for routine clinical work. The value of this simple test in cases of liver disease and also in patients undergoing clinical anaesthesia with the use of the muscle relaxant suxamethonium is also emphasized.

We are grateful to Dr. H. Lehmann, of St. Bartholomew's Hospital, for his helpful advice in the preparation of this paper. Generous supplies of the test-paper "acholest" were kindly provided by the Österreichische Stickstoffwerke Aktiengesellschaft, Linz/Donau, Austria. The test-paper is now obtainable from Miles Laboratories Ltd., Nuffield House, 41–46 Piccadilly, London W.1.

D

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MARSUPIALIZATION OF BARTHOLIN'S CYSTS

BY

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Bartholin's cysts have been treated for many years by total excision and are still so dealt with in many clinics. This procedure is sometimes regarded as a minor gynaecological operation and simple to perform, but difficulties are often encountered in practice. Troublesome haemorrhage may arise: the cyst may be ruptured, causing difficulty in finding the correct layer of cleavage. The latter situation necessitates removal of the cyst and gland *in toto*. Obliteration of the remaining cavity is not always an easy task, and failure to do this can result in post-operative haemorrhage and delayed healing by second intention. The patient may suffer from painful scarring and discomfort. Loss of secretion may cause trouble should the opposite gland be malfunctioning—artificial lubricants are not always acceptable to the patient. When the cyst has been excised the recurrence rate is high and subsequent attempts to operate in a fibrosed area present considerable difficulties.

In the presence of infection, oedema of the surrounding tissues renders the dissection of the thick and friable cyst wall almost impossible, and if the surgeon enters the corpus cavernosum haemorrhage can be very severe indeed.

Excision of an abscess is therefore seldom undertaken while active infection is present; the delay in operating adds to the anxiety and discomfort of the patient.

Davies (1948) proposed a simple method of treatment of Bartholin's cysts aiming at restoration of the function of the gland. He treated 25 cases by incision close to the hymen in the region of the opening of the duct. The cavity of the cyst was then packed with iodoform gauze, which was removed and replaced twice weekly for three weeks. The packing was to prevent the small incision from closing and to permit epithelization of the new ostium with squamous epithelium. The method was not always successful, and there was difficulty in maintaining a stoma even with continuous drainage for several weeks, because retraction of the wall of the cyst occurred as the inflammation subsided, permitting union across the opening.

Jacobson (1950) described the simple operation of marsupialization with construction of a new mucocutaneous junction, and reported 19 cases showing good results. A second series of 140 patients who had 152 cysts with only four recurrences was reported later

(Jacobson, 1960). The results were excellent in all cases, including three of the recurrences in which marsupialization had to be repeated. The reason for the few recurrences which did occur was thought to be inadequate incision. After Jacobson's original report, Tancer, Rosenberg, and Fernandez (1956) reported 11 cases treated by marsupialization, all with satisfactory results, and Blakey (1958), in this country, treated eight cysts and six abscesses with complete success.

The satisfactory results obtained by these authors, by performing an operation which appears to be free of complications and unique in restoring the function of the gland, made us consider treating our cases the same way. The possible advantages were obvious and we were in fact rewarded with similar success.

Anatomical Considerations and Technique

Although the lesion is called Bartholin's cyst or abscess, it is in fact a cyst or an abscess of the duct of the gland. This structure is able to distend as it traverses the loose connective tissue between the gland proper and the ostium. The gland itself is a homologue of Cowper's gland and lies deep to the bulbocavernosus muscle and the bulb, on the deep transverse perineal muscle (Fig. 1). It cannot become cystic as it is surrounded by resistant layers.

FIG. 1

FIG. 2

FIG. 1.—Right Bartholin's cyst. Appearance of vulva before operation. FIG. 2.—Appearance at end of operation.

In treating our cases we used the technique described by Jacobson, and paid particular attention to the length of the incision. A vertical incision 1 in. (2.5 cm.) long was made direct into the cyst, immediately lateral to the hymenal ring. The lining of the cyst was then grasped with Allis's forceps in order to avoid retraction, and the cyst emptied of its contents digitally, all pockets being opened (Fig. 2). The cavity was then washed out with normal saline, and the edges of its lining were sutured to the adjacent cut skin margin. Usually six sutures were required, using fine catgut on an atraumatic needle.

Results

Twelve operations have been performed over a period of two years. One was carried out in the casualty department, under local anaesthesia, and the patient was discharged home two hours later. Three of the patients were pregnant, one 30 weeks and the other two 24 weeks.

Three of the patients presented with recurrent cysts following previous attempts at total excision on the same side. Two of those had been operated upon twice. All patients had negative Wassermann and Kahn reactions and gonococcal complement-fixation tests. An abscess was present in two cases and culture of the pus grew *Staphylococcus pyogenes* on one occasion and an anaerobic streptococcus on the other. Chronic cysts were found in the remaining cases. One of these cysts was filled with blood clot, and the rest contained yellow purulent material, which did not grow any organisms when cultured. Histology of the lining in this case showed it to be typical duct epithelium.

All patients were immediately ambulant post-operatively and received a saline bath twice a day for the first three days and thereafter once daily. They were discharged two days after the operation, except for the three pregnant patients, who were kept in for four days to relieve them of any anxiety with regard to the pregnancy.

The patients were examined six weeks post-operatively and thereafter every three months for a year. We found that the cavity and original opening had shrunk to a considerable degree by the first follow-up visit, and on each of the following examinations only the nose of a small sinus forceps could be inserted. The sinus remained very small, but was in no case occluded at the end of the year. There were no complications and no recurrences.

Discussion

Marsupialization of Bartholin's cyst has many advantages over excision. The operation is simple; complications and recurrences are rare. If need be, recurrence can be dealt with by repeating the procedure. There is no post-operative discomfort, healing is rapid, and the stay in hospital is brief. The physiological function of the gland is retained.

If desired, marsupialization may be performed on out-patients under local anaesthesia. The fact that the procedure can be carried out on an acute Bartholin's abscess is of particular value, as the abscess is drained and the curative operation performed at the same time.

For these reasons we no longer find any place for excision in the treatment of Bartholin's cyst.

Summary

Ten cases of Bartholin's cyst and two of Bartholin's abscess were treated by marsupialization with complete success.

The simplicity of this operation and its advantages over the excision of the cyst are discussed.

I thank Professor J. C. McClure Browne for help and encouragement, and Mr. W. G. MacGregor and Mr. J. D. Murdoch for allowing me to operate on their cases.

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A revised British Standard Specification for *p*H scale (B.S. 1647:1961) has been issued. Copies may be obtained from the British Standards Institution, Sales Branch, 2 Park Street, London W.1, price 4s. 6d. each, postage extra to non-subscribers.

Preliminary Communications

Enteral Infection with Pasteurella Pseudotuberculosis

Isolation of the Organism from Human Faeces

Until 1954 human infections with *Pasteurella pseudotuberculosis* were thought to be rare. Masshoff (1953) described an abscess-forming reticulocytic ileocaecal lymphadenitis. The causative organism was identified by Knapp (1954) as *P. pseudotuberculosis*. Since then reports of some 200 cases have been published. The first cases in Great Britain were described by Mair *et al.* (1960). For further information about these infections see the extensive study by Knapp (1959).

From the beginning it was thought that the pathological changes found were the result of an enteric infection, arising in the last portion of the ileum and resulting in an infection of the ileocaecal lymph nodes. This point of view was supported by Graber and Knapp (1955), who found, under a small mucosal ulcer in the ileum of one of their patients, an identical reticulocytic infiltration breaking through the muscular coat. They could trace this characteristic picture along the lymph pathways to the regional lymph nodes. A similar case was seen by Flamm and Kovac (1958). For further support of the enteral infection theory they fed cultures of *P. pseudotuberculosis* to laboratory mice. This gave rise to pathological changes in the mesenteric lymph nodes similar to those found in their patient.

The isolation of *P. pseudotuberculosis* from faeces of patients suffering from this form of ileocaecal lymphadenitis would in my opinion almost prove the enteric character of this infection. No mention of this isolation from human faeces could be found.

Experiments and Method

In preliminary studies mixtures of faeces and known quantities of *P. pseudotuberculosis* were cultivated on different media. The best results were obtained on desoxycholate–citrate–agar plates. Enrichment broth of different kinds gave no improvements. Accordingly the following method was adopted. A small amount of faeces is suspended in some 0.85% NaCl and inoculated on desoxycholate–citrate–agar plates (Difco B 274), which are incubated at 22° C. for five days. As the medium is not selective for *P. pseudotuberculosis*, all suspected colonies have to be tested in the usual way.

Results

With this method we investigated the faeces of 23 guinea-pigs known to be suffering from a spontaneous infection with *P. pseudotuberculosis*; in nine the micro-organism was recovered from the faeces—six times type I and three times type II. Up to the time of writing we had examined faecal specimens of five patients known to be infected with *P. pseudotuberculosis*. From the faeces of one patient *P. pseudotuberculosis* type Ia was isolated on the fifth and sixth post-operative days. All specimens of later date were negative. This patient, a 25-year-old man, was operated on for suspected appendicitis. The appendix proved to be normal, but the last portion of the ileum was thickened, oedematous, and fiercely reddened. In the ileocaecal angle many swollen infected lymph nodes were noted. Ileitis regionalis was suspected. The pathological changes in a lymph-node biopsy were those usually found around the focus of a lymphadenitis of Masshoff; there were no micro-abscesses. The serum taken on the day of operation agglutinated *P. pseudotuberculosis* type I strongly (titre 1:2,560). This micro-organism was also found in the excreta of a canary owned by the patient. It proved to be of the same type Ia.

Conclusion and Summary

Faeces in five patients known to be suffering from the lymphadenitis ileocaecalis of Masshoff were examined for *Pasteurella pseudotuberculosis* by means of inoculation on desoxycholate–citrate–agar plates (incubation for five days at 22° C.). *P. pseudotuberculosis* type Ia was isolated from one patient. Of 23 guinea-pigs with positive cultures from liver abscesses, the faeces were also positive in nine.

This seems to be the first time that *P. pseudotuberculosis* has been cultured from human faeces. It strongly supports the theory that the mode of infection is by the enteral route. This isolation may also be of importance for epidemiological studies.

I gratefully acknowledge the encouragement and advice given by Professor A. Ch. Ruys. I am indebted to the Central Bacteriological Laboratory and the Laboratory for Public Health in Rotterdam for their hospitality and technical assistance. Thanks are expressed to Dr. W. J. H. Schmidt, head of the surgical department. for permission to publish case-notes concerning the patient.

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Medical Memoranda

Anencephaly in a Mono-amniotic Twin

It is generally agreed that mono-amniotic twins are extremely rare, although it is possible that some cases are being missed (Wilson, 1955). In the case reported below the patient was delivered of mono-amniotic twins, one of which was normal and the other anencephalic. Two detailed reports of similar cases were found in the literature (Litt and Strauss, 1935; Wilson, 1955), and Dumoulin and Gordon (1959) have reported di-amniotic mono-chorionic twins, one of which was anencephalic.

Case Report

A primigravida aged 23 first attended the Belfast City Hospital antenatal clinic on June 26, 1959, in the 10th week of pregnancy. She was a normal healthy woman, and careful inquiry failed to reveal any history of congenital abnormality or familial disease among her own or her husband's relatives. Her mother was a twin. The husband was a healthy tradesman aged 22.

Pregnancy progressed normally, and the patient did not suffer any virus disease at any stage. At 30 weeks twins were suspected, and an *x*-ray examination showed that one twin was anencephalic while the other appeared to be normal. There was no hydramnios, and pre-eclampsia did not develop.

Labour began spontaneously during the 41st week, and after six hours the membranes ruptured and meconium-stained liquor drained. Four hours later the first twin was delivered with forceps because of poor progress in the second stage. Immediate vaginal examination revealed that the face of the anencephalic second twin had entered the pelvis. The expected second sac of membranes was not present. The infant was delivered by traction with the finger in the mouth aided by a little fundal pressure during a uterine contraction.

Examination of the placenta revealed a single sac surrounded by the chorion and amnion. The two cords were attached eccentrically to the foetal surface and were only ½ in. (1.3 cm.) apart. There was no trace of any

Details of Blood-grouping

	ABO	Rh Phenotype	Probable Genotype	MN	K	Fy^a	S	Le^a
Father	B	CCDee	CDe CDe	M	–	–	Not tested for these factors	
Mother	A_1	—	cde cde	M	–	+	+	–
Twin I	A_1	CcDee	CDe cde	M	–	+	+	–
,, II	A_1	CcDee	CDe cde	M	–	+	+	–

septum of membranes between the cords, and it was clear that there had been a single amniotic sac containing both twins.

The anencephalic twin was a freshly stillborn female weighing 5 lb. 12 oz. (2,610 g.). Post-mortem examination did not reveal any other deformities. The normal twin, also a female, weighed 6 lb. 7 oz. (2,920 g.) at birth and was healthy.

Blood-grouping of parents and infants was carried out and the findings are shown in the Table.

Comment

It is interesting that severe congenital deformity was found in as many as 9.2% of infants in the combined series of 142 mono-amniotic twin pregnancies collected and reported by Quigley (1935) and by Wilson (1955). This type of twinning is undoubtedly uniovular, and abnormality of one twin of a pair cannot be convincingly explained on a basis of direct hereditary genetic factors or on generalized intrauterine environmental conditions which, presumably, affect both twins equally.

Streeter (1930) suggested that local congenital abnormalities are due to disparity in the vitality of different tissues in the embryo. It is believed (Corner, 1955) that mono-amniotic twins must separate later than di-amniotic twins, because their separation must occur after a single embryonic disk has formed, thereby inducing the formation of a *single* amniotic cavity—that is, between the seventh and the fourteenth day. It is possible that separation at this later and more highly developed stage might disturb the growth or diminish the vitality of localized embryonic tissues, thereby increasing the incidence of localized congenital abnormalities, such as anencephaly, in mono-amniotic twins. Incomplete separation will, of course, give rise to a double monster, and it is well known that abnormalities of any of the component parts of double monsters are relatively common.

There is a very high foetal loss associated with mono-amniotic twinning, and this is mostly ascribed to inter-twining of the umbilical cords *in utero*. Quigley (1935) reported a loss of 68% in his collected cases.

My thanks are due to Mr. J. A. Price for permission to publish this case, which was admitted under his care.

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Megaloblastic Anaemia during Combined Phensuximide and Phenobarbitone Therapy

Megaloblastic anaemia is a rare complication of anticonvulsant therapy and has been described during the administration of phenytoin sodium and primidone (Badenoch, 1954; Gordin, 1958) and in patients receiving large doses of barbiturate (Hobson *et al.*, 1956; Calvert *et al.*, 1958; Chanarin *et al.*, 1960). Details are given below of an epileptic patient who developed megaloblastic anaemia while under treatment with phensuximide (N - methyl - α - phenylsuccinimide; "milontin") and phenobarbitone, a combination of drugs not previously associated with the development of megaloblastic anaemia.

Case Report

A 33-year-old unmarried woman had suffered from epilepsy from the age of 3 years. Anticonvulsant therapy was initiated with phenobarbitone in 1933; between 1946 and 1954 she received phenobarbitone 2 gr. (0.13 g.) daily and sodium phenytoin 3 gr. (0.2 g.) daily, and during the last three months of 1954 also had primidone 750 mg. daily. On December 21, 1954, she was admitted to another hospital with a severe degree of anaemia; she was transfused with 3 pints (1.7 litres) of blood and given folic acid, cyanocobalamin, and ferrous sulphate. Within three months her blood findings had returned to normal, and after seven months all haematinics had been discontinued. The epilepsy, however, was poorly controlled on phenobarbitone alone, and two and a half years later (August, 1957) she was admitted to the neurological unit of the Northern General Hospital, where investigations showed an epileptogenic focus in the right temporal lobe on E.E.G. but a normal cerebrospinal fluid and air encephalogram.

In considering further anticonvulsant therapy it was decided to avoid primidone and phenytoin because of the uncertain nature of the type of anaemia which had developed during previous treatment with these drugs. Phensuximide was chosen for trial, since there were no reports of this drug's administration having been associated with haematological disturbances. On August 6, 1957, treatment was started with phensuximide, 0.5 g. six times daily, and the dose of phenobarbitone was reduced to 2 gr. (0.13 g.) daily. Ten weeks later, on a routine out-patient visit, her epilepsy was controlled but she complained of the recent onset of exertional dyspnoea. The haemoglobin, which had been 12.9 g./100 ml. two weeks previously, had fallen to 6.4 g./100 ml. She was readmitted for further investigation.

The mucous membranes were pale but no other abnormalities were found on physical examination; the dietary history was satisfactory and there were no alimentary symptoms. Blood examination showed normochromic red cells with anisocytosis, poikilocytosis, and some macrocytosis. The sternal marrow was frankly megaloblastic and aspirated gastric juice contained hydrochloric acid. Serum vitamin B_{12} level (*Lactobacillus leichmannii* assay method without added cyanide) was 140 $\mu\mu$g./ml. (normal range, 120–810 $\mu\mu$g./ml., Girdwood, 1960) and the absorption of labelled vitamin B_{12} (methods of Heinle *et al.*, 1952; Schilling *et al.*, 1955) was normal, the faecal and urinary recoveries of radioactivity being respectively 16% and 19% of that contained in the 0.5 μg. oral dose. A folic acid absorption test (Girdwood, 1960) also gave normal results;

urinary output of folic acid after the 5-mg. subcutaneous dose was 1.31 mg. and after the 5-mg. oral dose 1.1 mg. (excretion index 84%). The faecal excretion of fat (12-day collection on unrestricted diet) averaged 3.3 g./day (normal range 2 to 7.2 g./day, Doig and Girdwood, 1960), and barium follow-through examination was negative. The results of liver-function tests were normal.

When the patient was told that she had again become anaemic she refused to continue with phensuximide but agreed to remain on phenobarbitone. On October 18 2 pints (1,140 ml.) of whole blood were transfused. During the next 10 days further treatment was withheld and there was no evidence of spontaneous haematological improvement. On October 28, 1.000 μg. of cyanocobalamin was given intramuscularly (part of the Schilling test); during the next 72 hours no significant alteration occurred in the serum iron concentration and the marrow remained unchanged; the peripheral blood findings were: Hb, 8.7 g./100 ml.; red cells, 2,590.000/c.mm.; packed cell volume, 25.5%; mean cell volume, 99 cubic microns; mean corpuscular haemoglobin concentration, 34.2%; reticulocytes, 1%; white cells, 3.800/c.mm. On October 31, 5 mg. of folic acid was given subcutaneously, and this was followed, 24 hours later, by an equivalent dose by mouth (part of the folic acid absorption test); thereafter the patient received orally 5 mg. of folic acid twice daily. Within 48 hours of the administration of folic acid there was a significant fall in the serum iron concentration, indicating the occurrence of a haematological response; the values at 0, 24, and 48 hours were 210, 148, and 83 μg./100 ml. respectively. The reticulocyte count on the sixth day of therapy was 20%, and on the thirteenth day the Hb had risen to 9.6 g./100 ml. and red cells to 3,110.000/c.mm.

On December 22, when her peripheral blood findings and sternal marrow were entirely normal, she was persuaded to resume her previous treatment with phensuximide and phenobarbitone; the epilepsy was adequately controlled on this regime, and with the continuance of folic acid therapy her blood findings at regular follow-up visits always remained normal. She committed suicide two years later in a state of reactive depression immediately after unexpected discharge from her employment. A necropsy was not performed.

COMMENT

Detailed investigation of this case failed to reveal a cause for the megaloblastic anaemia other than the anticonvulsant therapy. It is probable that the anaemia was induced by phensuximide either alone or in combination with phenobarbitone; the alternative possibility of phenobarbitone having been solely responsible for the anaemia is regarded as unlikely, as only one example of megaloblastic anaemia complicating phenobarbitone administration has been reported in the literature, and this occurred in a patient receiving large doses of the drug (Chanarin *et al.*, 1960). The absence of previous reports of megaloblastic anaemia occurring during phensuximide therapy may be related to the fact that this drug has been mainly used in the treatment of petit mal in children. In Great Britain megaloblastic anaemia is very rare in this age-group and there have been no reports of this type of anaemia complicating anticonvulsant therapy in children.

The severe anaemia which the patient developed in 1954 while receiving sodium phenytoin, primidone, and phenobarbitone may have been megaloblastic in type, but a more definite opinion cannot be given, as the marrow smears, made elsewhere at that time, were not available for study. None the less it appears that the patient's bone-marrow was unduly sensitive to anticonvulsant drugs. The megaloblastic anaemia which occurred during phensuximide and phenobarbitone therapy was refractory to cyanocobalamin but responded promptly to folic acid. This finding is in agreement with the hypothesis of Girdwood and Lenman (1956) and Chanarin *et al.* (1958) that megaloblastic anaemia due to anticonvulsant drugs does not result from tissue depletion of folic acid but arises from an interference with folic acid metabolism.

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Diabetic Xanthomatosis in an African

Diabetic xanthomatosis was first described by Addison and Gull (1851). Joslin *et al.* (1959) found only 14 cases among a series of 21,000 diabetic patients. Most recent accounts have been single case reports (McGavack and Shepardson, 1933; Thompson *et al.*, 1935; Combes and Behrman, 1941; Spencer, 1951; Margolin, 1953; Gumpel and Lipton, 1955; Kolb *et al.*, 1955; Bloom and Crowley, 1956; Grollman, 1956; Johnston, 1959).

CASE REPORT

On April 8, 1959, an African boy aged 14 was admitted to hospital. For 10 months he had suffered from polyuria, polydipsia, polyphagia, loss of weight, and lassitude. For nine months he had noticed pain, numbness, paraesthesiae, and weakness of his legs, which had rendered him bedridden by the time of his admission. For three months a rash had been present. Of special interest was his diet, which, typical of many rural Africans in these parts, consisted almost entirely of maize meal and meat, with no butter and very little milk.

Photograph showing skin lesions above the left elbow.

On admission he was extremely ill—unable to stand and almost too weak to move. He weighed 84 lb. (38.1 kg.) and had many of the stigmata of kwashiorkor: for example, oedema of the lower limbs and puffiness of the face; brownish, silky hair which had lost its normal coarse tight black curls; generalized depigmentation; and obvious wasting of the body. There was a papular eruption affecting mainly the

extensor surfaces of the body, superficially resembling pustules, with yellow centres and dark areolae. The individual papules varied in size from 1 to 5 mm. in diameter and were most marked on the knees and elbows (see illustration), but were also present on the shoulders, buttocks, and to a less extent the chest and face. The pulse was 75 and the B.P. 110/70. The only other positive findings were in the nervous system, where there was a peripheral neuritis affecting the lower limbs. The fundi showed lipaemia retinalis.

Investigations produced the following results:

	8/4/59	14/4/59	3/6/59	6/8/59
Blood:				
Haemoglobin (g./100 ml.)	13·0			
W.B.C. (per c.mm.) ..	8,300			
E.S.R. (Wintrobe) ..	53 mm.			
Fasting blood sugar (mg./100 ml.)		330		175
Blood urea (mg./100 ml.)	48		40	35
Serum proteins:				
Total (g. 100 ml.) ..	9·8		11·8	7·6
Albumin ,, ..	0·8		1·4	3·3
Globulin ,, ..	9		10·4	4·3
Alpha 1 (g./100 ml.) ..			0·7	0·7
,, 2 ,,			2·1	0·9
Beta ,,			4·9	1·0
Gamma ,,			2·7	1·7
A/G ratio	0·09		0·1	0·7
Serum lipids (g./100 ml.)	16·0			
Serum cholesterol (mg./100 ml.)	1,000		277	230
Phospholipids } ..	Results			
Lipoproteins }	mislaid			
Urine:				
Chemistry:				
Albumin	Nil	Nil		
Glucose (g./100 ml.) ..	2 or more	0·25		
Ketones		Nil		
Microscopy ..	N.A.D.			
Concentration and dilution test		Normal		

Histology of the papule from the knees: "Lipoid-laden histiocytes (foam cells) are present with some extracellular lipoid in the dermis."

For the first week soluble insulin was given six-hourly according to the amount of glucose in the urine, and potassium chloride 5 g. daily. Thereafter soluble insulin 60 units was given half an hour before meals. For the first month tab. aneurin. co. forte, 2 tablets t.d.s., were given. The diet chosen was one we felt the patient would be able to continue once he returned home; it consisted of three more or less equal meals, each composed of meat, soup, maize meal, and a few green vegetables.

Within 24 hours of admission the urine was free of ketones. In three days the milkiness of the serum cleared and the lipaemia retinalis disappeared. After three weeks the minute papules on the face and chest were no longer visible, while the larger papules had decreased in size and lost their yellow centres. However, even when the patient was discharged after four months, the larger papules were still visible as small shiny keloid scars. After one month the puffiness of the face had gone, but the minimal oedema of the feet and ankles was still present after two months. A month after admission the patient was able to walk, the sensory abnormalities having improved, but the foot-drop was still present at the time of discharge. In spite of losing the oedema his gain in weight was spectacular, being 84 lb. (38.1 kg.) on admission, then 93, 100, 110, and 115 lb. (42.2, 45.4, 49.9, and 52.2 kg.) on successive weeks. After two months he weighed 130 lb. (59 kg.) and 132 lb. (59.9 kg.) when discharged four months after admission.

COMMENT

In Thannhauser's (1949) classification diabetic xanthomatosis falls into the group of secondary xanthomatoses in the course of diabetes mellitus due to hyperlipaemia. Insulin acts at various levels in carbohydrate and fat metabolism (Chernick and Chaikoff, 1951; Stadie, 1957). Characteristically the diabetic state is associated with the frequent occurrence of lipaemia and hypercholesterolaemia. In diabetic lipaemia the emphasis is on the neutral fat fraction while the cholesterol and phospholipid fractions are increased less or not at all (Hirsch *et al.*, 1953). Hirsch *et al.* (1953) have found that the hyperlipaemia bears a parallel relationship to the blood-sugar levels, while Tuller *et al.* (1954) and Johnston (1959) have shown no precise relationship between the hyperglycaemia and hyperlipaemia. Tuller *et al.* (1954), however, have shown a general relationship between the serum lipid deviation and the degree of acidosis.

Probably, in simple terms, the hyperlipaemia represents an increased mobilization of fats from the tissue depots in an attempt to supply the energy requirements of the body from fatty acid and ketone body oxidation.

This case is of particular interest for several reasons: (*a*) it supports the predominant male incidence (Combes and Behrman, 1941); (*b*) it shows the condition in its extreme form, as could be seen only in a primitive person seeking attention at the last moment; (*c*) it demonstrates that the fat content of the diet is not important in the causation of the entity or its treatment; (*d*) it illustrates the progress of the skin lesions in Africans who are prone to keloid formations; (*e*) it shows xanthomatosis in association with peripheral neuritis, which was thought to be diabetic rather than due to malnutrition, owing to its slow and incomplete response to vitamin therapy; (*f*) it was associated with oedema, which was thought to be due to hypo-albuminaemia and a kwashiorkor-like state, and possibly to a less extent a trophic change due to the peripheral neuritis; (*g*) it showed gross abnormalities of the serum proteins, especially the alpha-2 and beta-globulin fractions, the more detailed analysis of which was lost, but which probably represented lipoproteins as previously shown by Bloom and Crowley (1956); and (*h*) it shows that this rare complication does also affect Africans in whom diabetes itself is considered rare (Gelfand, 1957).

I thank the Director of Medical Services, S. Rhodesia, for permission to publish this article; the late Dr. E. G. Weyhausen for the clinical photograph; and many others for their help and advice.

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Reviews

ANOREXIA NERVOSA

Anorexia Nervosa. Its History, Psychology, and Biology. By Eugene L. Bliss, M.D., and C. H. Hardin Branch, M.D. (Pp. 210+vii. No price.) New York: Paul B. Hoeber, Inc. 1961.

No physician who has dealt with patients suffering from anorexia nervosa can fail to be interested in this uncommon symptom of psychological disorder. It is therefore a pleasure to find that Dr. Eugene Bliss and Dr. Hardin Branch, of the psychiatric department of the University of Utah, have written an engrossing monograph on the condition.

The book begins with a chapter on the history of our knowledge of the disorder, beginning with seventeenth-century accounts of subjects who must have suffered from it. Its emergence as a clinical entity dates from 1873, when it was described almost simultaneously by Sir William Gull, of Guy's Hospital, and by Dr. Charles Lasèque, professor of clinical medicine in Paris. Gull employed the term "anorexia nervosa," which has become the accepted name in the English-speaking world. He noted that the subjects were usually young women who, in addition to emaciation, were likely to have amenorrhoea, a slow pulse, and constipation; there was no detectable bodiiy disease: in spite of their wasted bodies the patients were restlessly active. Gull attributed the absence of appetite to "a morbid mental state," while the peculiar liability of young women to be the victims of the disorder was dealt with as follows: "That mental states may destroy appetite is notorious, and it will be admitted that young women at the ages named are specially obnoxious to mental perversity."

Clinical aspects of the condition are next described on the basis of the literature and of the authors' own studies of 22 patients. Then follows an account of the underlying psychodynamics of the failure to eat adequately. One point that emerges is that these patients often have an excellent appetite, even to the point of being ravenous, but they rigidly control it, though they may on occasion behave like gluttons. For some of them eating is sinful and starvation correspondingly virtuous. The authors review the various psychological mechanisms which have been suggested to account for this behaviour, such as the psycho-analytical explanation of the condition as an oral manifestation of sexual behaviour, but conclude that there is usually a complex network of experiences which dictates the unconscious choice of alimentary difficulties by these subjects.

The secondary manifestations of the disorder are those of slow starvation, and the book contains a valuable chapter which is replete with references to the literature on these.

So far as treatment is concerned, the essential aim is the obvious one of getting the patient into a mental state in which she wishes to eat normally. This aim, and one way of how not to achieve it, comes out plainly in one of the patient's own words: "The dietitian insisted on telling me in detail what I should eat and it was all I could do to keep from screaming at her, 'The problem is very simple: I don't want to eat.'" The various treatments which have been advocated are reviewed, and it is plain that success can be achieved by totally opposed approaches to the problem. Some physicians, such as the late Sir Arthur Hurst, have achieved excellent results by domineering methods—for example, by ordering the patient to eat in their presence and insisting that she does so—while others have done well by appearing to ignore any necessity for the patient to eat. Presumably the way the patient reacts to her physician must be of crucial importance, but this is the very aspect of therapy hardest to assess, especially when an "organic" or drug-method of treatment is being employed by a physician who does not believe in psychotherapy, but who inevitably employs it, even if unconsciously, if he is any good as a doctor.

In brief, this is an engaging account of a group of subjects whose lives are dominated by food just as much as are those who find expression for their difficulties in eating to the point of becoming extremely obese. As one of the authors' own patients has put it: "But I can always find release in food. It is my complete servant, or should I say I am food's complete slave. Nevertheless, through food I can find a substitute for any punishment or satisfaction of which I am in need."

S. C. Truelove.

ANGIOGRAPHICAL CLASSIC

Angiography. Edited by Herbert L. Abrams, M.D. Foreword by Henry S. Kaplan, M.D. Volumes 1 and 2. (Pp. 461+xvi; illustrated. Pp. 465–807+vii; illustrated. £17.) London: J. and A. Churchill Ltd. 1961.

These two volumes are timely and welcome. Dr. Abrams, the editor, has done a grand job in bringing together all forms of angiography—pulmonary, aortic (thoracic and abdominal), coronary, cerebral, renal, peripheral, and even adrenal, pancreatic, hepatic, splenic, uterine, and venous (pulmonary and systemic). This is a remarkable achievement. Each main section describes the development of the method, the technique itself as practised at the present time, the hazards involved, and the diagnostic value of the procedure. The angiograms themselves are all first rate, and a great deal of care has gone into their selection and preparation.

The standard throughout is uniformly excellent. Helpful line drawings of the vascular anatomy accompany the angiograms in all sections. The cerebral section by Greitz and Lindgren is particularly illuminating, but then so is the section on thoracic aortography by Abrams and Jönsson, pulmonary angiography by Dotter, abdominal aortography by Rogoff, and renal angiography by Olsson.

The injection of contrast medium into any part of the circulation has proved to be one of the greatest advances ever made in the cardiovascular field; the impact of the work under review will resolve any doubt about that. One can but thank and congratulate the authors on their meritorious work, and the editor in particular for having the vision and practical ability to assemble all this in one piece. It is likely to prove the world's first angiographical classic.

Paul Wood.

SALIVARY GLANDS

Physiology of the Salivary Glands. By A. S. V. Burgen, M.D.(Lond.), M.R.C.P., and N. G. Emmelin, M.D.(Lund). (Pp. 279+vii; illustrated. 35s.) London: Edward Arnold (Publishers) Ltd. 1961.

The salivary glands have lent themselves to experimental investigation over centuries, largely because their topography renders this relatively easy. Despite the ease and intensity with which they have been studied their physiology still contains many unsolved problems. In the last 40 years this study has been increased, partly

because new methods have been available—for example, isotopes, pure active principles, electronic recording—but also new concepts of function—for example, the interaction between neural and chemical control of function.

It is clear, therefore, that the time is ripe for a stock-taking of this subject. Both Dr. Emmelin, of Lund, and Dr. Burgen, of McGill, are by reason of their work and experience and contacts in a better position to do this than anyone else in present-day medicine. The result is, as one might expect, a clear statement of all aspects of the subject, the histology and anatomy, the experimental physiology and pharmacology of the gland, the composition of saliva, the metabolism and salivary control in the intact animal, together with the role of saliva in the intact organism (including some lesser-known functions), and in the comparative field.

There is nothing startlingly new or unexpected, but there is a clear statement of the present position of our knowledge and the evidence for that position. This monograph will be of value to those working or about to work in this field and for those studying or teaching physiology for higher degrees.

A. St. G. Huggett.

ACUTE POISONING

The Medical Management of Acute Poisoning. By Gordon Cumming, B.Sc., Ph.D., M.B., Ch.B., A.R.I.C. With a chapter on the Psychiatric Aspects of Poisoning by Myre Sim, M.D.(Ed.), D.P.M. (Pp. 128+ix. 10s. 6d.) London: Cassell. 1961.

This small book is well written and has several features which make it stand out from the more conventional manuals on poisoning. Almost one-third of the text is about the effects of poisoning on respiration, circulation, and renal function. The four common poisons (carbon monoxide, barbiturates, salicylates, and alcohol) are then considered in separate chapters. In each there is a good account of the way in which the poison acts. This makes the treatment section easier to follow. There are short chapters on other poisons and on poisoning in children.

A few minor criticisms may help to improve the next edition. It is not made clear that bemigride is the same as "megimide"; the trade name for safety containers is "kiddi-pruf," and a swallowed poison need not be called a "toxic ingestant." Ohlsson's "blood lavage" (accelerated diuresis) technique is not generally accepted and should have either more space or none. The details of cardiac massage are too brief to be of practical value.

The continued care of the rescued patient is of great importance. Dr. Myre Sim discusses this in his nine pages on "The Psychiatric Aspects of Poisoning." The information and advice given are not usually found outside books on psychiatry. There are four pages of suggestions for further reading.

This book is not one to be consulted at the last minute, but should be studied before the emergency arises. It is confidently recommended to all physicians.

C. Allan Birch.

MEDICAL MYCOLOGY

Atlas of Medical Mycology. By Emma Sadler Moss, B.S., B.M., M.D., and Albert Louis McQuown, B.S., B.M., M.D. Second edition. (Pp. 335+xi; illustrated. 88s.) London: Baillière, Tindall and Cox, Ltd. 1960.

This is more than an atlas of mycology, though as such it is admirable. Clinical and especially mycological features are illustrated in black-and-white with a few coloured plates.

This is the second edition of this useful work, which will be of value to student and practitioner. Fungous infections of skin and mucous membranes are increasing in this country, partly from increased travel and community life, partly as a side-effect of medical treatment. There are also the occasional patients with deep mycoses with which we shall probably become increasingly familiar.

There is a glossary of terms followed by a broad but simple classification which will help those without special knowledge of this subject. The text is adequate and lucid, covering botanical details, with short reference to clinical features, treatment, and prognosis. The great majority of the illustrations are very good.

The individual groups of fungi are dealt with in twenty chapters. In addition, there are valuable chapters on techniques, on the recognition of contaminants, and on immunology.

This is a very practical work, admirably presented at reasonable price, and can be recommended to clinical and laboratory workers.

John T. Ingram.

MUNICH RADIOLOGY CONFERENCE PROCEEDINGS

IXth International Congress of Radiology (Proceedings). Vols. I and II. Edited by B. Rajewsky. (Pp. 1,625; illustrated. DM. 240.) Stuttgart, George Thieme Verlag, Munich and Berlin: Urban and Schwarzenberg. 1961.

The proceedings of the ninth international congress of radiology held in Munich in July, 1959, are now published in two volumes and run to over 1,600 pages and about 1,000 illustrations. Even so, only about one quarter of the papers are published in full, the remaining three-quarters being printed as abstracts. The business meetings and the opening and closing ceremonies are also included. The scientific work is divided into seven sections: diagnosis; therapy; nuclear medicine and supervoltage therapy; radiobiology and biophysics; radiation protection; physics and technique; and justice and law, economy, teaching, and research in radiology.

Radiology covers such a large field nowadays that it is impossible for any one individual to have an up-to-date grasp of all aspects. The scope of the work and the size of radiological international congresses have now become far too large.

The two volumes under review are well published in the best German tradition, but one doubts if many private individuals will be prepared to spend about £20 to buy them. The papers are published in German, English, French, or Spanish, the official languages of the congress.

J. W. D. Bull.

CURRENT AMERICAN THERAPY

Current Therapy, 1961. Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D. (Pp. 806+xxxii. 87s. 6d.) Philadelphia and London: W. B. Saunders Company. 1961.

This volume, edited by Dr. Howard F. Conn, now appears in its thirteenth edition, and will no doubt be welcomed as a work of reference by many practitioners in the U.S.A. It is doubtful, however, whether a volume of this type has much attraction for general practitioners in this country, but medical school libraries should always find a place for it.

The pattern of the work is unchanged, and consists of 307 contributions by nearly as many authors, each chapter being the expression of the personal practice of the individual physician. This system inevitably leads to repetition and overlap, seen particularly in the section on the respiratory system, where 15 authors contribute 17 articles. Many minor and some major surgical conditions are discussed, but too often on such a superficial plane that one wonders for whom the note has been written. In contrast, acute renal failure is discussed in less than one page, poison ivy dermatitis in two, fistula-in-ano requires nearly five pages of discussion, and haemorrhoids another six. Many important aspects of obstetrics are covered, but it is surprising that only 14 pages are devoted to the neuroses and to the whole of psychiatry in a volume of over 800 pages. A very full account of parenteral fluid therapy in adults is given, which contains much wisdom, but the article is concealed in the section on the digestive system. Some of the therapeutic advice in the endocrine section demonstrates that a few authors unfortunately still fail to see any virtue in thyroxine as a preferable alternative to thyroid *U.S.P.*

The book gives an interesting insight into current and individual practices in different parts of the United States, and reference to it can occasionally clarify the treatment of obscure conditions. The British reader may feel, however, that a more fully integrated concept of therapeutics is of greater value.

A. G. Macgregor.

SURGERY OF BILIARY PASSAGES

Chirurgie des Voies Biliaires, Extra- et Intra-Hépatiques. By Claude Olivier. (Pp. 611+x; illustrated. 100 NF.) Paris: Masson et Cie. 1961.

This book on the surgery of the extra- and intra-hepatic biliary passages is one of the Henri Mondor series of surgical monographs which are published by Masson et Cie, of Paris. It is a most attractive book of over 600 pages, yet not bulky. It is well printed on thin paper of good quality. Dr. Claude Olivier himself deals well and thoroughly with the whole subject of the surgery of the biliary passages, with chapters on hydatid disease of the liver by Professor F. Bourgeon and the surgical aspects of neonatal jaundice by Professor G. Laurence. It is clearly written and excellently illustrated, with all pictures drawn to a common pattern by the same artist, giving it a smooth uniformity.

It is divided into seven parts: anatomy, investigation, radiomanometry, and so on, constitute Part 1; the surgery of biliary lithiasis Part 2; biliary obstruction Part 3; tumours Part 4; and chronic affections—including stenosing odditis, hydatid disease, cysts of the biliary passages, and so forth—Part 5. Spontaneous fistulas occupy Part 6, a matter of only 21 pages; and the emergency surgery of the biliary passages the last part.

As a whole, the book is an erudite and complete study of the orthodox and it has been a pleasure to read it. The index, however, is far too brief, details of such operations as sphincteroplasty and transduodenal biliary drainage are inadequate, and guidance in such difficult subjects as related biliary obstruction and portal hypertension is not given. I hope these defects will be repaired in subsequent editions.

Alan H. Hunt.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Uveitis and Toxoplasmosis. By E. S. Perkins, Ph.D., M.D., F.R.C.S. (Pp. 142+ix; illustrated. 30s.) London: J. and A. Churchill Ltd. 1961.

Ciba Foundation Study Group No. 8. Problems of Pulmonary Circulation. (Pp. 96+viii; illustrated. 12s. 6d.) London: Churchill. 1961.

Congenital Malformations of the Heart. 2nd edition. Vol. I, *General Considerations.* Vol. II, *Specific Malformations.* By Helen B. Taussig, M.D. (Vol. I: Pp. 204+xxvi; illustrated. Vol. II: Pp. 1,049+ix; illustrated. 120s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1961.

Inhaled Particles and Vapours. Proceedings of an International Symposium organized by the British Occupational Hygiene Society, Oxford, March 29 to April 1, 1960. Edited by C. N. Davies. (Pp. 495+viii; illustrated. £5.) London: Pergamon Press Ltd. 1961.

Exploring Inner Space. Personal experiences under LSD-25. By Jane Dunlap. (Pp. 216. 21s.) London: Victor Gollancz Ltd. 1961.

Formation and Breakdown of Haemoglobin. Proceedings of the Symposium held in Leeds, March 26, 1960. Edited by C. P. Stewart. (Pp. 71; illustrated. 15s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. New York, Toronto, London: D. Van Nostrand Company. 1961.

Provision of Laboratory Animals for Research. By W. Lane-Petter. (Pp. 147+xii; illustrated. 20s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. New York, Toronto, London: D. Van Nostrand Company. 1961.

A Christian Therapy for a Neurotic World. By E. N. Ducker. (Pp. 225. 21s.) London: George Allen and Unwin Ltd. 1961.

Essentials of Electrocardiography. By Lieutenant-Colonel N. S. Variava, M.D., M.S. (Pp. 72; illustrated. Rs. 10.) Bombay: Current Technical Literature Co. Private Ltd. 1961.

Medical Department United States Army in World War II. Vol. V. Communicable Diseases Transmitted through Contact or by Unknown Means. Prepared and published under the direction of Lieutenant-General Leonard D. Heaton. Edited by Colonel John Boyd Coates, jun., M.C., Ebbe Curtis Hoff, Ph.D., M.D., Phebe M. Hoff, M.A. (Pp. 530+xxiii; illustrated.) Washington, D.C.: Office of the Surgeon General, Department of the Army. 1960.

Die Thromboembolischen Erkrankungen. By Professor Dr. Th. Naegeli, Doz. Dr. P. Matis, Professor Dr. R. Gross, Professor Dr. H. Runge, and Professor Dr. H. W. Sachs. (Pp. 1,045+viii; illustrated.) Stuttgart: Friedrich-Karl Schattauer-Verlag. 1960.

Klinische Chirurgie für die Praxis in vier Bänden. Band II, Lieferung 2. By Professor Dr. med. O. Diebold, Professor Dr. med. H. Hunghanns, Professor Dr. med. L. Zukschwerdt. (Pp. 232; illustrated. DM. 43.50.) Stuttgart: Georg Thieme Verlag. 1961.

Klinische Elektrokardiographie. By Professor Dr. Max Holzmann. 4, Erweiterte und verbesserte Auflage. (Pp. 889+xv; illustrated. DM. 87.) Stuttgart: Georg Thieme Verlag. 1961.

Abdominal Operations. By Rodney Maingot, F.R.C.S. With special articles by 36 British and American contributors. 4th edition. (Pp. 1,402+xviii; illustrated. £10 10s.) London: H. K. Lewis. 1961.

Nurse has Four Cases. By Elizabeth Avery. (Pp. 188. 15s.) London: Michael Joseph. 1961.

The Vesico-Vaginal Fistula. By J. Chassar Moir, C.B.E., M.D., M.A., D.M., F.R.C.S.Ed., F.R.C.O.G. (Pp. 151+vii; illustrated.) London: Baillière, Tindall and Cox. 1961.

Psychotherapeutic Techniques in Medicine. By Michael and Enid Balint. (Pp. 236+xvi. 21s.) London: Tavistock Publications. 1961.

The Physiological Regulation of Salivary Secretions in Man. A Study of the Response of Human Salivary Glands to Reflex Stimulation. By Alexander C. Kerr. International Series of Monographs on Oral Biology. Vol. 1. (Pp. 86; illustrated. 40s.) Oxford: Pergamon Press. 1961.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY OCTOBER 14 1961

CHRONIC BRONCHITIS AND THE GENERAL PRACTITIONER

To the sufferer from chronic bronchitis the season of mists and mellow fruitfulness is one of ill omen. After the relief of the summer months he begins to feel his chest tightening. His phlegm increases, and before the winter is out he is likely to have spent a week or more in severe distress at home in bed. His family doctor will be anxiously aware that about 27,000 persons die yearly from bronchitis in England and Wales.

This disease undoubtedly presents general practitioners with "a most frequent and intractable problem," as the report from the College of General Practitioners published in the opening pages of the *Journal* this week asserts, and it is one which it is encouraging to see the College tackling in an original way. The fact that a random sample of patients by age and sex could be drawn throughout the country is a tribute to the organization of the Ministry of Health and its executive councils and provides a precedent that will be noted by others interested in measuring the prevalence of disease. The technique that enabled the observations of 90 doctors to be standardized so that the individual doctor's clinical assessments could be compared also breaks new ground. The report's chief lesson to the general practitioner in his management of the patient is the manifest effect of cigarette smoking, which has often been emphasized previously.[1-4] Less than 2% of men with the "standard diagnosis" of chronic bronchitis in this report had never smoked. The most important contribution that the practitioner can make to the prevention of this disease is to persuade his patients—at least those with a smoker's cough—not to smoke cigarettes. He will do this more readily if he does not smoke himself. Those who cannot stop smoking may be much better off with a pipe than with cigarettes. Most established bronchitics are also greatly improved by giving up their cigarettes. There is some evidence that buffered lobeline tablets may help to tide over the first few days of deprivation,[5,6] but they probably cannot do more than that.[7] This survey also confirms that the well-known gradients of mortality from bronchitis between the social classes and between urban and rural areas are real and not due to diagnostic bias or to differences in smoking habits. The indication that bronchitis may be less fatal and disabling in women than men supports the impressions of clinicians and the results of other surveys.[8] We shall look forward to further information from the more complete analysis of the results of this survey promised in the present report.

The main causes of disablement in the established case are recurrent bouts of infection and dyspnoea due to obstruction of air flow in the bronchi, and these are the symptoms that the practitioner strives to relieve. Since there is chronic infection in most cases it is not surprising that attempts to raise resistance with vaccines have been unsuccessful,[9,10] but exacerbations of the infection can be controlled by antibiotics. The questions then are: Which drug should be used? and, Should it be given prophylactically throughout the winter or therapeutically at the time of each exacerbation? Two reports in to-day's *Journal* (pp. 979 and 985) confirm that penicillin is of uncertain value either prophylactically or therapeutically unless culture of the sputum shows a predominant infection by pneumococci. The exceptional success of penicillin in a previous trial[11] may have been due to an unusual prevalence of pneumococci in the winter of 1958–9. Sulphonamides have never been shown to have any significant effect.[10] On the other hand the tetracyclines have repeatedly been shown to give benefit, though 0.5 g. daily[11] may not be sufficient. Demethylchlortetracycline ("ledermycin") may be the most effective of these and has the advantage that only two daily doses are required.

Exacerbations of bronchitis have been reduced in severity and frequency by both prophylactic use of tetracycline throughout the winter[10,12-16] and therapeutic administration at the time of each attack.[17-19] The former procedure has the disadvantage of expense and of causing troublesome gastro-intestinal disturbance occasionally; the latter requires that the drug be prescribed immediately at the onset of an

[1] Higgins, I. T. T., *Brit. med. J.*, 1959, **1**, 325.
[2] Ibid., 1959, **1**, 351.
[3] Ibid., 1960, **2**, 1077.
[4] Olsen, H. C., and Gilson, J. G., ibid., 1960, **1**, 450.
[5] Bartlett, W. A., and Whitehead, R. W., *J. Lab. clin. Med.*, 1957, **50**, 278.
[6] Rapp, G. W., Dusza, B. T., and Blanchet, L., *Amer. J. med. Sci.*, 1959, **237**, 287.
[7] *Brit. med. J.*, 1961, **1**, 586.
[8] Fletcher, C. M., Elmes, P. C., Fairbairn, A. S., and Wood, C. H., ibid., 1959, **2**, 257.
[9] Brown, H. M., and Wilson, R. N., ibid., 1959, **1**, 263.
[10] Edwards, G., Buckley, A. R., Fear, E. C., Williamson, G. M., and Zimmerman, K., ibid., 1957, **2**, 259.
[11] British Tuberculosis Association, ibid., 1960, **1**, 297.
[12] Buchanan, J., Buchanan, W. W., Melrose, A. G., McGuiness, J. B., and Price, A. U., *Lancet*, 1958, **2**, 719.
[13] Moyes, E. N., and Kershaw, R. A., ibid., 1957, **2**, 1187.
[14] Helm, W. H., May, J. R., and Livingstone, J. L., ibid., 1956, **1**, 775.
[15] May, J. R., and Oswald, N. C., ibid., 1956, **2**, 814.
[16] Murdoch, J. McC., Leckie, W. J. H., Downie, J., Swain, R. H. A., and Gould, J. C., *Brit. med. J.*, 1959, **2**, 1277.
[17] Elmes, P. C., Fletcher, C. M., and Dutton, A. A. C., ibid., 1957, **2**, 1272.
[18] Moyes, E. N., and Kalinowski, S. Z., *Tubercle* (*Lond.*), 1959, **40**, 112.
[19] Berry, D. G., *et al.*, *Lancet*, 1960, **1**, 137.
[20] *Brit. med. J.*, 1961, **1**, 1019.
[21] Huguley, C. M., jun., Erslev, A. J., and Bergsagel, D. E., *J. Amer. med. Ass.*, 1961, **177**, 23.
[22] Wright, B. M., and McKerrow, C. B., *Brit. med. J.*, 1959, **2**, 1041.

exacerbation. Since the patient may not call his doctor until he is already very ill some patients have been given tablets to start taking at the first sign of a "chest cold." The recent trial by the British Tuberculosis Association[11] confirms previous observations that this technique is often foiled by the patient's inability to recognize the onset of his attacks of infection—though in some more intelligent patients it works very well. The key to diagnosis is development of purulent sputum or fever. Some patients may have persistently purulent sputum which can be rendered mucoid by continuous administration of tetracyclines and they may be much improved by this means.[14 15] When tetracycline fails to control the purulence of sputum after two or three days of adequate dosage (1–2 g. per day) chloramphenicol is almost always effective and its administration should not be delayed in seriously ill cases. It is, of course, unsuitable for continuous or repeated administration because of the danger of aplastic anaemia,[20] except for occasional patients who cannot be helped by any other drug. Repeated platelet and reticulocyte counts or estimations of serum iron may be carried out in such cases.[21]

Renunciation of smoking and control of infection may reduce bronchial secretions sufficiently to relieve dyspnoea, but most patients need a bronchodilator. Ephedrine (⅜ grain or 25 mg.) may be combined with sodium amytal (¼ grain or 50 mg.) to relieve the tremor or agitation sometimes experienced, or it may be prescribed in the resinate form to give a more prolonged effect, particularly during the night. The various preparations of modified aminophylline may give additional relief by mouth or by suppository. An aerosol of adrenaline or isoprenaline administered by hand inhaler or pressure capsule is better than any other form of bronchodilator for most patients. There is no evidence to support the canard that these aerosols perpetuate bronchospasm. Though only a few bronchitic patients benefit from corticosteroids, the benefit is so great in these few that a trial is often worth while, especially in patients with much wheezing and uninfected sputum. The difficulty lies in assessing the results of a trial, for so many patients feel subjectively better when they take these drugs. It is wise to measure the ventilatory capacity several times before starting the drug (the Wright peak flow meter[22] successfully used in the general practitioners' survey is usually sufficient) and then again after a few days' treatment with, say, 5 mg. of prednisone q.d.s. If there is no change in the ventilatory capacity the tablets can be stopped. If the patient feels better, dummy tablets may be substituted for a further few days to confirm the subjective nature of the improvement. If the ventilatory capacity is improved the dose should be reduced gradually to the least that gives adequate relief of the dyspnoea. As little as 2.5 mg. of prednisone daily is often strikingly helpful.

Various simple measures must not be overlooked. Postural drainage for a quarter of an hour in the morning and evening may greatly lessen expectoration when sputum is profuse. The British habit of sleeping with open windows in the coldest of weather must be discouraged; a warm bedroom may make a great deal of difference. In foggy weather a few drops of ammonia in a saucer sufficient to maintain a very faint aroma appears to relieve many patients who are susceptible to fog, and it can do no harm. A useless cough disturbing sleep can usually be controlled by an adequate dose of codeine: syrup of codeine 5–10 ml. or tablets of ½–1 gr. (30–60 mg.) is usually effective (codeine linctus contains so little of the drug as to be almost useless). No other form of antitussive has yet been shown to be better than codeine. Practitioners who set about stopping their patients from smoking, control their infections, and lessen their dyspnoea and cough, especially in the early stages, may arrest the progress of this disease while they relieve its distressing symptoms.

CLINICAL USEFULNESS OF ALDOSTERONE ANTAGONISTS

Though the initial enthusiasm for regarding aldosterone as the sole substance concerned with the physiological and pathological retention of sodium in the body has cooled, the aldosterone antagonists have proved to be of use in the treatment of oedematous patients. In heart failure the mechanism of sodium retention is still obscure, but is possibly related to deranged renal haemodynamics.[1] Aldosterone probably plays little part. The cause of oedema in nephrosis and cirrhosis is better understood. It results, in part at least, from the effect of aldosterone on the renal tubules. The secretion of this hormone in excessive amounts in these diseases can be regarded as a device for re-expanding plasma volume.

Retention of sodium leads to retention of water and ultimately to clinically apparent oedema, since sodium is normally retained with its osmotic equivalent of water. Reabsorption of sodium takes place in at least three places during the passage of the glomerular filtrate along the renal tubule: osmotic reabsorption in the proximal tubule; active reabsorption in the loop of Henle; and further

reabsorption in exchange for hydrogen and potassium ions in the distal tubule under the influence of adrenal steroids, of which aldosterone is the most important.

Excessive reabsorption of sodium at the proximal tubule can be countered by the administration of conventional diuretics of mercurial or thiazide type. Little is gained, however, if all the sodium which escapes through the proximal tubule is reabsorbed in the distal tubule under the influence of aldosterone. It would seem logical, therefore, to attempt to block proximal reabsorption of sodium with "conventional" diuretics and to block distal reabsorption with aldosterone antagonists.

Clinically useful results have attended this line of attack. As might be expected, the most striking success has been attained in conditions where the rate of secretion of aldosterone is excessive—namely, in hepatic cirrhosis and the nephrotic syndrome. In hepatic cirrhosis the administration of the aldosterone antagonist spironolactone alone has resulted in a worth-while diuresis, with loss of weight in some cases,[2-4] but a much more efficient sodium diuresis is obtained by the simultaneous administration of a thiazide diuretic, such as chlorothiazide, with spironolactone.[3-6 8] Similar success has met combined therapy in patients with the nephrotic syndrome[5-7]; again, some patients respond well to spironolactone alone.[7] The treatment of patients with congestive heart failure has not been so successful, as might be expected, since the role of aldosterone in the sodium retention of this condition is debatable. Patients with ischaemic heart disease tend to respond better than patients with chronic rheumatic heart disease. Few of these patients have a clinically worth-while response to spironolactone alone, but some respond well to simultaneous treatment with a thiazide or mercurial diuretic plus spironolactone.[5-7]

When spironolactone is administered a delay of 24 hours or so elapses before a diuretic effect is obtained. Treatment with this agent must therefore be continued for several days if satisfactory results are to be obtained. Five-day courses are often adequate for out-patients. Since spironolactone is expensive, there is no advantage in its use if a mercurial or thiazide diuretic produces an adequate diuresis. The great merit of spironolactone is that it is frequently effective in producing a diuresis in patients who have become resistant to conventional diuretics. In these patients it is rarely effective alone, but may produce a diuresis when given in the usual dose of 400 mg. daily in conjunction with a thiazide diuretic, such as chlorothiazide (1 g. daily), and if this combination does not produce the desired effect the addition of mersalyl (2 ml. daily) will often result in a worth-while diuresis. In some patients 800 mg. of spironolactone produces a much greater effect than the normal dose of 400 mg. This combination of the three drugs is probably the most potent diuretic broadside at present available.

Most diuretics, particularly those of thiazide type, tend to increase the excretion of potassium as well as that of sodium; this can quickly lead to hypokalaemia. Spironolactone blocks the potassium-losing action of aldosterone. The simultaneous administration of spironolactone with a thiazide or mercurial diuretic considerably reduces the loss of potassium encountered when these diuretics are administered alone. But potassium can still be lost when the two types of diuretic are used together, particularly during the first few days. This, plus the observation that a potassium supplement increases the sodium-diuretic effect of this combination,[8] warrants the administration of potassium to bring the total daily intake up to about 100 mEq (7.4 g.). The varnished tablets are absorbed better than the enteric-coated. Many patients with cirrhosis have very poor appetites and their intake of potassium is low. As appetite improves with successful treatment the need for supplementary potassium is reduced. The situation is different in the case of patients with congestive heart failure, who have some degree of renal impairment, often a raised blood urea, and difficulty in excreting potassium; hyperkalaemia can attend the administration of spironolactone, either alone or in association with other diuretics.[9] Potassium supplementation is obviously contraindicated in these circumstances.

The prolonged administration of spironolactone in combination with other diuretics and a low-sodium diet may result in hyponatraemia, since sodium is excreted in excess of its equivalent of water. When this occurs the administration of a non-sodium-retaining glucocorticoid, such as prednisone, with spironolactone may promote loss of sufficient "free" water (i.e., water in excess of its iso-osmotic amount of sodium) to restore the concentration of sodium in the plasma while enabling a diuresis of sodium to continue. If the oedematous patient when first seen

[1] Vander, A. J., Wilde, W. S., Malvin, R. L., and Sullivan, L. P., *Amer. J. Med.*, 1958, **25**, 497.
[2] Vesin, P., *et al.*, *Bull. Soc. Méd. Paris*, 1959, **75**, 826.
[3] Clowdus, B. P., Higgins, J. A., Rosevear, J. W., and Summerskill, W. H. J., *Proc. Mayo Clin.*, 1960, **35**, 97.
[4] Shaldon, S., McLaren, J. R., and Sherlock, S., *Lancet*, 1960, **1**, 609.
[5] Edmonds, C. J., ibid., 1960, **1**, 509.
[6] See *The Clinical Use of Aldosterone Antagonists*, edited by F. C. Bartter, 1960. Charles C. Thomas, Springfield.
[7] Slater J. D. H., Moxham, A., Hurter, R., and Nabarro, J. D. N., *Lancet*, 1959, **2**, 931.
[8] Ross, E. J., *Brit. med. J.*, 1961, **1**, 1508.
[9] Manning, R. T., and Behrle, F. C., *J. Amer. med. Ass.*, 1961, **176**, 769.

suffers from hyponatraemia the combination of spironolactone and prednisone is worth trying initially, and a thiazide or mercurial diuretic can be added later when the concentration of sodium in the plasma has risen to normal.

It will be seen that treatment of cirrhosis, nephrosis, congestive heart failure, or other forms of resistant oedema with a combination of conventional diuretic and aldosterone antagonist is not to be undertaken lightly, since a close watch on the concentrations of plasma electrolytes is required, particularly in patients with renal impairment or patients who are also under treatment with digitalis derivatives. Nevertheless, with suitable supervision the lives of many water-logged patients can be made bearable by treatment along these lines, though of course it has no influence on the progress of the underlying disease.

Side-effects of spironolactone therapy are few. Patients sometimes complain of drowsiness. Hirsutism has also been reported. Occasionally hepatic coma has developed during spironolactone therapy, but there is no clear evidence that it was a direct complication of the treatment. Theoretically, a rise of blood ammonia could result from the effect of spironolactones in decreasing the production of hydrogen ion in the renal tubules, since this will reduce the amount of hydrogen ion available for combination with ammonia to form ammonium ion for excretion in the urine. Hyponatraemia can produce a clinical picture resembling that of hepatic pre-coma.

HYPERTENSION OF PREGNANCY

Theories abound concerning the specific hypertensive disease of pregnancy, but a satisfactory explanation of the mechanism of the raised arterial pressure is still awaited. In this connexion two recent publications by C. A. Hunter and W. F. Howard[1 2] are of considerable interest, though not everyone would agree with all the conclusions. The authors report that samples of amniotic fluid drawn from patients with hypertension in pregnancy caused contraction of the rabbit aortic strip,[3] whereas samples from normotensive patients had negligible effects. Decidual extracts and various plasma samples from the hypertensive cases also contracted the aortic strip. The several materials active on the aortic strip were found to raise the blood-pressure on intravenous injection into the cat. Hunter and Howard believe that all these effects are due to a peptide, which they have named "hysterotonin." They consider that the decidua of the hypertensive cases contains an enzyme which acts on the proteins of the plasma or amniotic fluid to form this peptide.

These findings are interesting, and may well be important, though much more needs to be known before their significance may be assessed. It is not clear, for example, that all the effects seen are due to a single substance. One specimen of amniotic fluid caused slow contraction of the aortic strip, a response which suggests to Hunter and Howard the formation of the active peptide by enzyme action in the bath itself. Injection of the same amniotic fluid into the cat, however, gave only a sharp response, similar to that from the peptide angiotensin; there was no slow component as would have been expected had a vasoactive peptide been formed from the plasma proteins of the cat by enzyme action. The apparent discrepancy could be explained by the hypothetical enzyme being inactive on cat substrate, but no information is provided on this point. A more serious defect is the almost complete lack of quantitative information on the activity found. The authors apparently did not measure the effects against a standard preparation of the active material, and their results may have been influenced by alterations in the sensitivity of the aortic strip.

It is to be hoped that the problems can be overcome and accurate quantitative data provided on the levels of pressor material found in plasma and amniotic fluid of a wide range of normal and hypertensive women. Until these facts are known the significance of the present findings is uncertain. It might also be preferable for the present to avoid the neologism "hysterotonin." If the effects are due to a newly recognized peptide, deferring the baptism can do little harm. The premature naming of pharmacological actions can, however, do much to retard progress, and a misnomer can hardly ever be eradicated. In the same field the archaic and confusing terminology of the so-called "toxaemias of pregnancy" has persisted over the years, though it has done little other than provide this aspect of obstetrics with an aura of obscurity.

[1] Hunter, C. A., and Howard, W. F., *Amer. J. Obstet. Gynec.*, 1960, **79**, 838.
[2] —— —— ibid., 1961, **81**, 441.
[3] Furchgott, R. F., and Bhadrakom, S., *J. Pharmacol. exp. Ther.*, 1953, **108**, 129.

ATROPHIC POLYCHONDRITIS

Reports of systemic diseases primarily affecting cartilage are rare and, when the congenital diseases are excluded, extremely rare. Owing to the cosmetic effect of the cartilage in the ear and nose and its mechanical effect in the larynx and trachea the lesions resulting from such disease are unlikely to be overlooked, and the rarity of the published cases therefore probably correctly reflects their low incidence.

During the past 40 years fewer than 20 cases have been published under a variety of names such as polychondropathia, chondromalacia, and panchondritis. Features they have in common are an inflammatory swelling and softening of the cartilage of the ear and respiratory tract as well as an arthritis of variable extent

[1] Davies, H. R., and Kelsall, A. R., *Ann. rheum. Dis.*, 1961, **20**, 189.
[2] Thomas, L., *J. exp. Med.*, 1956, **104**, 245.
[3] Bryant, J. H., Leder I. G., and Stetten, D., jun., *Arch. Biochem.*, 1958, **76**, 122.
[4] Lack, C. H., and Rogers, H. J., *Nature (Lond.)*, 1958, **182**, 948.

and severity. In addition some of the patients have developed an iritis and episcleritis leading occasionally to blindness. The systemic nature of the disease is also suggested by the raised sedimentation rate and fever. In a recent paper H. Rhys Davies and A. R. Kelsall[1] briefly summarize the previously published cases and report the first in Great Britain in some detail under the title atrophic polychondritis. In addition to the features shown by most of the previous cases Davies and Kelsall's patient gave a positive Rose–Waaler test, thus suggesting a relationship to rheumatoid arthritis. A biopsy of the external ear taken during the active phase of the disease showed invasion of the cartilage with subdivision by fibrous bands fairly heavily infiltrated with lymphocytes and plasma cells.

The aetiology of the condition is entirely obscure, though the widespread softening of cartilage recalls the similar widespread condition produced in rabbits by the intravenous injection of papaine.[2] This powerful proteolytic enzyme apparently hydrolyses the linkage between chondroitin sulphate and the protein in cartilage to which it is bound, the result being rapid and extensive elution of the polysaccharide, much of which can be subsequently detected in the urine.[3] In this experimental condition, as in the human disease, respiratory obstruction may result from the softening and collapse of the tracheal cartilage rings. Whereas in Davies and Kelsall's case clinical improvement followed treatment with A.C.T.H., in the experimental animal the normal recovery was delayed or inhibited by cortisone. A further distinction of some importance is the absence of any significant inflammatory cell reaction in the experimental lesion. Nevertheless the softening and collapse of the cartilaginous structures in atrophic polychondritis may well be the result of local protease activity, since C. H. Lack and H. J. Rogers[4] have shown that the serum fibrinolysin, plasmin, can produce essentially the same result as papaine. It would therefore be of great interest in any future case to study the blood level and urinary excretion of chondroitin sulphate and its metabolites.

FROM STUDENT TO NURSE

The demand for nursing staff continues to exceed the supply, and it has been estimated that student nurses in training for the General Register make up nearly half of the staff in hospitals taking acute and mainly acute cases. Nursing is said to be the major example of a profession which continues to train its new recruits in this country through an apprenticeship system with little or no recourse to outside educational institutions, and the training is obviously a fruitful field for study—which it has not lacked of recent years. The value of the final examination for registration was recently questioned in these columns.[1] Now an interesting report has appeared on the other end of the student nurse's course—the first six months. Experience shows that this is the crucial period; it is the time when the proportion falling out is highest.

The Oxford Area Nurse Training Committee[2] has published the results of a survey carried out during the first six months of training by Mrs. Jillian MacGuire in five schools. It aimed at providing information under four headings—the training programme, the background of the entrants, their attitudes and motivations, and their adjustment to ward situation. The avowed object of the preliminary training school is to enable the candidate to obtain a grounding in the essential scientific subjects and practical skills before entering the hospital wards, but there is reason to believe that sometimes the school is too much divorced from the hospital, and the period spent there used to break the back of teaching in anatomy and physiology for the State examination rather than to introduce the student to hospital atmosphere. All but 15% of the entrants in this study had had at least one year of schooling above the minimum leaving age. Over one-third had qualifications that would have gained them a place in a teacher's training college, while 5% or 6% could have been considered for a university place. Nearly half of the student nurses in the survey had been in paid employment in a hospital at some time before beginning formal training, usually as medical auxiliaries, cadets, or pre-preliminary training school pupils. The principal motivation in the choice of nursing was a desire to help other people; the results to be achieved were felt to be more immediate and more recognizable than the results of work done by other groups in the welfare service. Choice of training hospital was often governed by its reputation. When seen within one month of joining the training school more than half of the girls hoped to work in a hospital abroad or in the Forces, on board ship, or as air hostesses. While nearly all the student nurses expected to have some difficulty in adjustment to the environment of the ward most of them looked forward to starting work in the wards, for practical work was regarded as "real" nursing.

When seen after they had been working in the wards for a month three-quarters of the girls had no doubt that nursing was the right choice for them, though about half had experienced some difficulty in finding out what was expected of them in their first ward. Seventeen per cent found the accommodation provided in hospital "not very good"; 8% disliked the attitude of senior nursing staff to juniors; 7% were dissatisfied with pay or hours of work (the split-shift system was not popular); 4% were depressed by the fact that there were some patients they could do little to help.

The recommendations arising from this study were grouped under three main headings—acceptance of candidates for training, organization of the preliminary school, and introduction to the ward. It recommends that candidates should be provided with fuller information about conditions of service before embarking on training and that the practice of requiring a student nurse to sign a contract of service with the hospital should cease; registration as a student should take the

[1] *Brit. med. J.*, 1961, 2, 635.
[2] *From Student to Nurse.* Oxford Area Nurse Training Committee, 43 Banbury Road, Oxford. 5s. 1961.

place of a contract. The preliminary school should be more closely integrated with the main school and hospital. The period at the preliminary school should be reduced at least to eight weeks and in it more emphasis should be placed on practical work. If possible, prophylactic injections and vaccinations and Mantoux tests should be carried out before the student enters the preliminary school. A new student nurse should always work with one more senior during her first few days in the ward. Tutorial supervision for at least the first three months in the ward should be given by the tutor who supervised the nurse in the preliminary school. Plans of the lay-out of the hospital and of each ward should be prominently displayed, and there should be a procedure book and a work list on each ward to which the student nurse can refer. The split-shift system should be replaced by a straight shift. It is hoped at a later date to review the whole of the training period of the same group of student nurses.

PSYCHOGENIC PAIN

It will readily be agreed that individuals vary in their tolerance of pain. Physical pain due to comparable organic lesions may be tolerated very differently by different individuals, and organic pain can often be accentuated by tension and anxiety. Furthermore, anxiety may have physical effects on the human organism which in turn give rise to pain. Tension headaches resulting from persistent contraction of the occipito-frontalis and posterior neck muscles are a good example. But many patients, and even doctors, find it difficult to accept that pain can be the result of an emotional disturbance and that no demonstrable physical mechanism need be responsible for this symptom. Pain of emotional origin has long been referred to as hysterical, but A. Walters,[1] in a recent review, gives reasons why, in his view, the term "hysterical" should be discarded and the descriptive title "psychogenic regional pain" preferred.

Walters suggests that pain can be experienced as a form of somatic hallucination involving different parts of the body in patients suffering from many forms of neurosis and psychosis. This pain syndrome is usually a manifestation of subconscious fear or of a state of personal danger, real or imagined, while it may develop after physical injury when all physical cause for pain has disappeared. The latter course of events is, of course, particularly common when the question of financial compensation is involved.[2] Analysing 430 cases, of which more than two-thirds were female and less than one-third male, Walters found that the commonest sites of pain were the head and neck, chest and upper limbs, and lower back, though virtually any area of the body could be affected. Continuous burning pain in the upper jaw (atypical facial neuralgia) in middle-aged women is one of the commonest symptoms. In many cases the pain resulted from fear of cardiac infarction or brain tumour and superficially resembled the pain resulting from the condition in question; this was particularly common when there had been a family history of one or other of these complaints. Often some such factor could be found which determined the site of the pain. Other characteristic features were the bizarre and histrionic descriptions given to these pains ("grinding pressure" or "like a vice") along with their variability and inconsistency, both of character and of location, in many cases. Commonly there was associated motor weakness of "hysterical" type, hyperalgesia, or anaesthesia failing to correspond to any anatomical demarcations in the limb or other part of the body where the pain occurred. Even the tendon reflexes may be altered in the affected limb.

As Walters points out, recognition of the nature and cause of psychogenic regional pain is not usually difficult if the history taken is complete, if a full picture of the patient's conditions of life can be obtained, and if care is taken to inquire about other symptoms of an emotional character, such as anxiety, depression, and tension. Treatment along simple psychiatric lines, including reassurance about the absence of serious organic disease and an explanation of how the symptoms arose, reinforced if need be by drugs, is often remarkably successful.

[1] Walters, A., *Brain*, 1961, **84**, 1.
[2] Miller, H., *Brit. med. J.*, 1961, **1**, 919, 992.

PILL AT F.P.A. CLINICS

In its recent statement (see page 1032) on the contraceptive pill the Family Planning Association is wise to emphasize the need for careful supervision of patients. Progestogen-oestrogen pills upset a primitive biological mechanism, and as has been said recently[1] in this journal "it still remains to be shown that the suppression of ovulation over long periods is harmless to the endocrine system and to ovario-uterine relations." Data needed to understand fully the possible hazards of long-term administration are at present lacking, a fact recognized in the F.P.A.'s recommendation of "closely studied research" in this direction. Its medical staff are to be specially trained in the method and the pills will be administered only in suitable cases. It is worth bearing in mind that many women will be unsuitable for a variety of reasons. One of these, which is true of most contraceptive methods, is that a certain amount of intelligence and persistence are needed for it to be effective. Another is that the side-effects in a few cases may be more severe than the woman will put up with. Patients will have to understand that the pill is a potent drug that has to be prescribed with care and continued vigilance.

NEW OFFICE FOR DR. CHARLES HILL

In the new Government changes announced this week Dr. Charles Hill, formerly Chancellor of the Duchy of Lancaster, is to be Minister of Housing and Local Government and Minister for Welsh Affairs, with a seat in the Cabinet.

[1] *Brit. med. J.*, 1961, **2**, 754.

Clinicopathological Conference

A CASE OF SEVERE RHEUMATOID ARTHRITIS

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a woman with severe rheumatoid arthritis and anaemia who died at the age of 63 in Hammersmith Hospital (Case No. 209,571; P.M. No. 8,399).

Clinical History

Dr. A. St. J. Dixon: This patient first noted arthritis of the knees, feet, and ankles, which later spread to the hands, shoulders, and elbows, in 1939, when she was aged 44. She attended various spas and clinics in the subsequent years and had numerous physical and medical treatments, including three courses of gold injections, each with temporary improvement. A fourth course of gold had to be stopped because of toxicity—possibly agranulocytosis.

I first met her in 1950 when she was admitted to the Canadian Red Cross Memorial Hospital at Taplow. She was a pleasant, accomplished person with severe and crippling rheumatoid arthritis (Fig. 1) and much destruction of subarticular bone on *x* ray. The heart and lungs were normal, as were the haemoglobin and white cell count. The differential agglutination test (D.A.T.) for rheumatoid arthritis was positive, and there were changes in the plasma proteins which gave a thymol turbidity of 10+ units and a colloidal gold test of 5 units. She was treated mainly with bed rest followed by graded physiotherapy, and did well for a while. In 1951 and in 1952 she was given courses of corticotrophin injections, but these were stopped because of three haematemeses. In 1951 she was investigated at University College Hospital for a macrocytic anaemia unresponsive to all haematinics. I am indebted to Dr. Hugh Burt for details of her investigations at University College Hospital. A sternal marrow biopsy in 1951 showed no definite megaloblasts, but a few of the intermediate normoblasts were slightly deficient in nuclear chromatin. In 1953 and in 1954 in University College Hospital various subluxed lateral toes were amputated because of pressure lesions of the skin.

Febrile Deterioration

In April, 1954, she was again admitted to University College Hospital for deterioration of arthritis, with fever (up to 102° F.—38.9° C.) and wasting. By this time she had become bedridden, and was found to have pericarditis (both a friction rub and E.C.G. changes), anaemia (haemoglobin 68%, colour index 1.06, mean corpuscular volume 103 c.μ, mean corpuscular haemoglobin concentration 30%). She also had enlargement of the liver and spleen, and a sore throat, dry mouth, and inflamed eyes. *X*-rays showed some enlargement of the cardiac shadow, with small bilateral pleural effusions, and generalized osteoporosis. A fat balance was normal. Two lupus-cell preparations were negative; nevertheless a presumptive diagnosis of lupus erythematosus was made, and cortisone, 100 mg. daily, was given with improvement. Pericarditis and fever settled and large nodules on the occiput were reduced in size, but she developed radiological evidence of an apical lung lesion, presumed to be tuberculous, and which resolved after a course of para-aminohippuric acid with isoniazid. Although crippled, she was able to get about a little.

Severe Anaemia

In 1955 she was readmitted to University College Hospital for breathlessness due to severe anaemia. The haemoglobin was 31%, the mean corpuscular volume 110 c.μ, and a white cell count 1,400 per c.mm. The blood film and marrow were typical of pernicious anaemia, and responded to injections of "cytamen" (cyanocobalamin), the reticulocytes rising to 5.5% and the haemoglobin to 102%. The liver and spleen were again noted to be palpable, although soft.

Between 1955 and 1958 she was nursed at home by her husband. She was light and frail and he was reasonably strong so that it was possible for them to manage. Maintenance treatment was by cortisone 37.5 mg. every day, and injections of vitamin B_{12} every third week. She became increasingly bedridden. In 1958 her husband developed severe pain in his back and thigh, with wasting of the thigh muscles and loss of left knee-jerk due to prolapse of the third lumbar intervertebral disk, and he was unable to manage. Because of this the patient (and her husband) were admitted to Hammersmith Hospital.

The previous history was of rheumatic fever at the age of 15 without residual heart lesions. There had been intermittent diarrhoea since 1947, which had been thought to be due to faecal impaction. The family history was negative for rheumatic disease, but there was a striking family tendency to pernicious anaemia, the father, paternal grandfather, paternal aunt, and possibly a brother all having had this disease.

Clinical Findings

On examination she was pale, thin, exceedingly crippled with flexion deformities of the limb joints. The changes in the hands were now much more advanced (Fig. 2), and there was a curious dystrophy affecting the nails, which did not (with one exception) grow in length, but in thickness only, building up as thickened, irregular, horny masses which ultimately shed, the process then

LEGENDS TO SPECIAL PLATE

Fig. 1.—Right hand, showing changes due to rheumatoid arthritis when seen in 1950.

Fig. 2.—Same hand in 1958, showing the progression of the deformity and the changes in the nails.

Fig. 3.—Radiograph of hand, showing advanced rheumatoid arthritis.

Fig. 4.—One of the fingers removed after death and cut in sagittal section, showing radiograph on the left and necropsy specimen on the right.

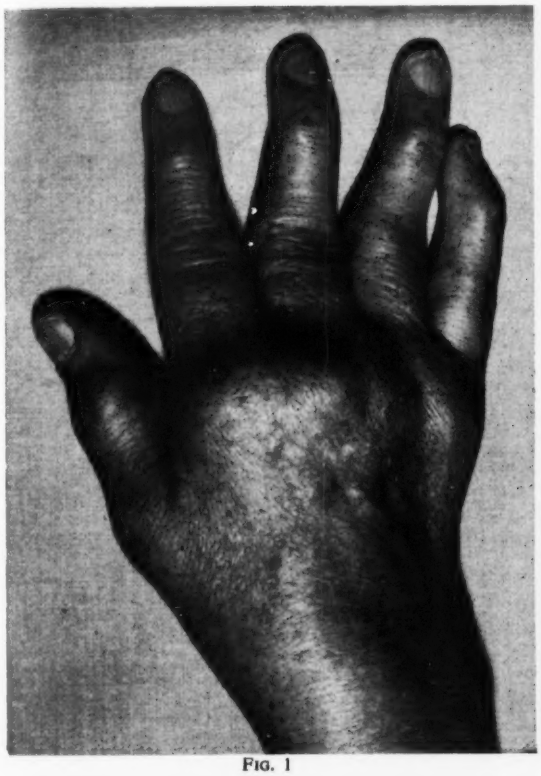


Fig. 1

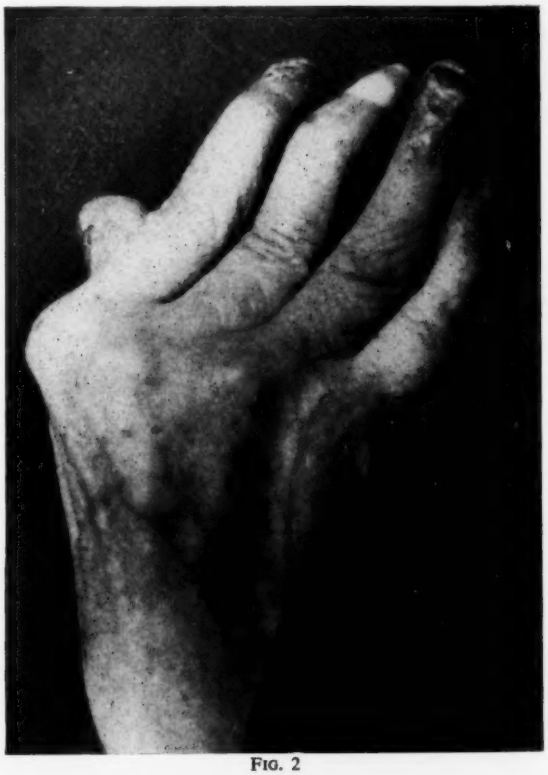
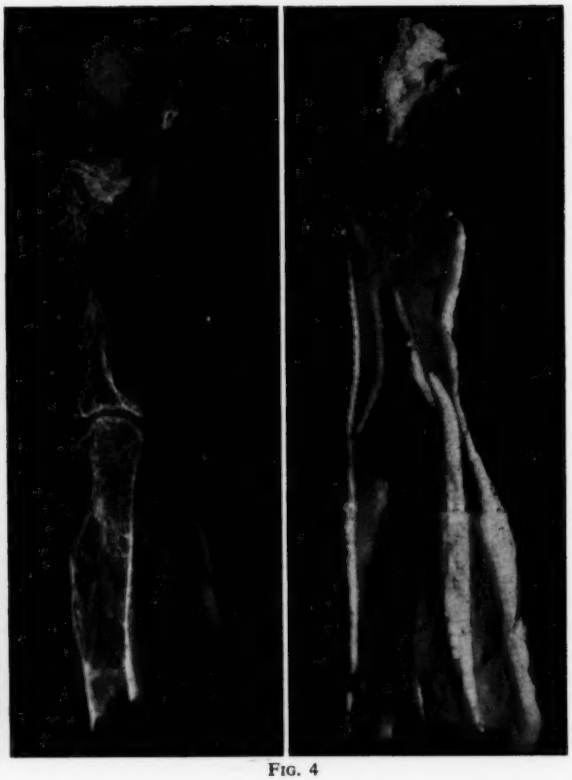


Fig. 2

Fig. 3



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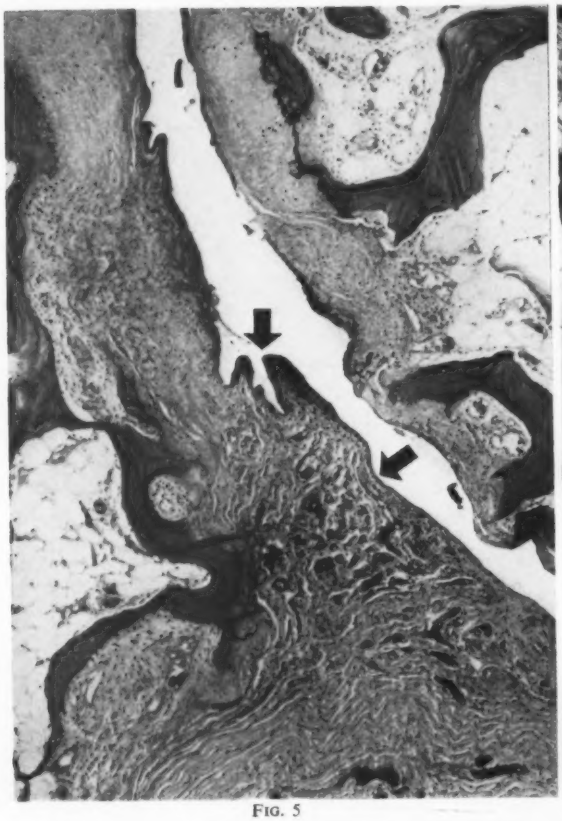


Fig. 5

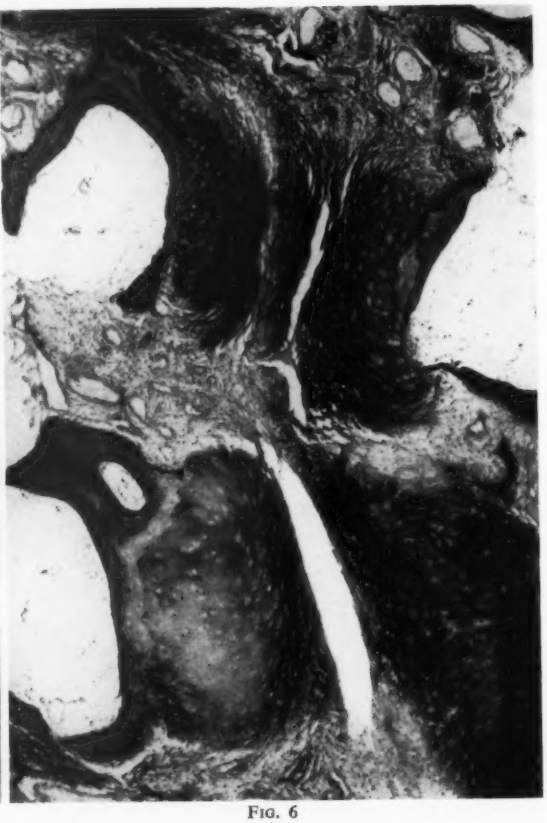


Fig. 6

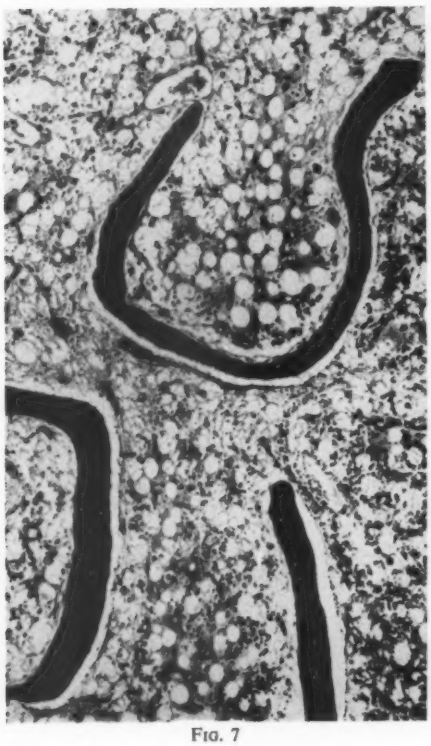


Fig. 7

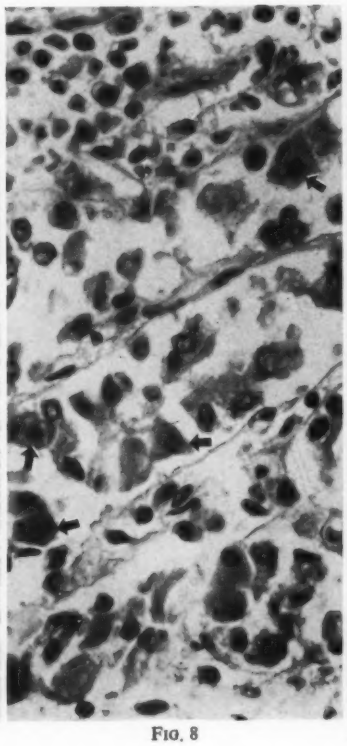


Fig. 8

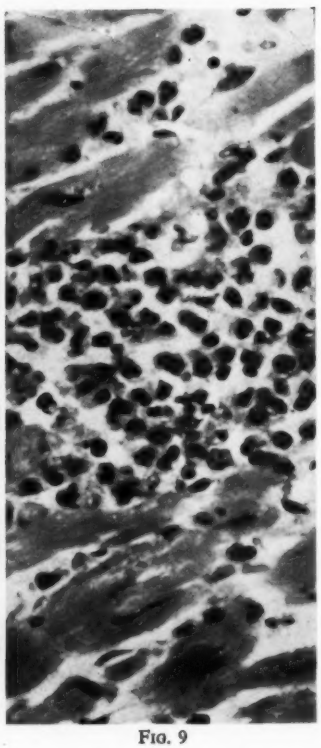


Fig. 9

starting again. The knees showed flexion contractures, the muscles were generally wasted and feeble, the skin was papery and atrophic, and there was oedema of the lower legs. There were rheumatoid nodules on both elbows. The spleen was enlarged, being palpable about 4 cm. below the costal margin, and the lymph nodes in the neck and axillae were also enlarged. There was a tender mid-thoracic kyphosis and, possibly because of this, the abdomen appeared protuberant. The central nervous system, the heart, and the lungs were normal.

On investigation, she was found to be slightly feverish (up to 100° F.—37.8° C.) with a rapid sedimentation rate (135 mm. in one hour, Westergren). The blood picture was that of a typical iron-deficiency anaemia (haemoglobin 53%, mean corpuscular haemoglobin concentration 27.5%). The serum iron was 28 μg./100 ml. The white cell count was 14,000, with a normal differential count. The plasma proteins were—total 9.1 g. (albumin 3.1 g., globulin 6 g.). The serum calcium was 4.4 mEq/litre, phosphate 1.6 mEq/litre, alkaline phosphatase 22.5 units/100 ml. The zinc sulphate test was 19 units and thymol turbidity 15 units; the D.A.T. was again positive. The intravenous congo red test for amyloid was negative. Occult blood was frequently present in the stools. No lupus erythematosus (L.E.) cells were present, but the fluorescent antinuclear test for L.E. factor was positive. (L.E. factor is found in practically all cases of lupus erythematosus, and in a small proportion of patients with rheumatoid arthritis.) Radiographs showed the changes of severe rheumatoid arthritis in the hands (Fig. 3), and also spinal osteoporosis with collapse fractures of the bodies of the second lumbar and sixth thoracic vertebrae.

SUBSEQUENT PROGRESS

At first she made good progress. With ordinary rehabilitation measures, graded exercises, and serial splints for the knee contractures, she began to sit up in one week, and to get out of bed and stand with assistance in one month. Her anaemia responded to a course of intravenous iron injections, with a 6.4% reticulocytosis and haemoglobin rising to 78%. Her painful kyphosis improved with anabolic steroids (testosterone and oestradiol given together). There were gains in weight and strength.

Unhappily, after six weeks the patient acquired a ward respiratory infection and from then on nothing went well. She developed a basal pneumonia, only partially responding to antibiotics and to increasing corticosteroid therapy to prednisolone 15 mg. per day. During this time she lay immobile and rapidly lost weight. Despite nursing attention, frequent turning, and a "ripple" bed, she developed enormous, painful, progressively enlarging bed-sores, which later became infected with antibiotic-resistant staphylococci. Her weight fell to 75 lb. (34 kg.). In view of her painful state with poor prognosis, all attempts at treating her various infections were stopped, and she was kept as comfortable as possible with analgesics. She died with bronchopneumonia on April 26, 1958, aged 63.

LEGENDS TO SPECIAL PLATE

FIG. 5. — Metacarpo-phalangeal joint showing fibro-vascular pannus growing over edge of articular surface (between arrows). (H. and E. ×60.)

FIG. 6.—Interphalangeal joint showing destruction of articular cartilage in centre with erosion of underlying bone. A fibrous adhesion joins the articular surfaces at this point. (Picro-Mallory. ×60.)

FIG. 7. — Vertebral osteoporosis with slender bone spicules. (H. and E. ×56.)

FIG. 8.—Gastric mucosa showing oxyntic cells (arrows). (H. and E. ×505.)

FIG. 9.—Miliary abscess in myocardium. (H. and E. ×510.)

Clinical Diagnosis

(1) Severe rheumatoid arthritis.
(2) Pernicious and iron-deficiency anaemias.
(3) Possible portal cirrhosis.
(4) Osteoporosis and crush fractures of vertebrae.
(5) Bronchopneumonia.
(6) Bedsores.

Post-mortem Findings

Dr. J. G. AZZOPARDI: This was a wasted, elderly woman with white hair. There were ulcers with sharply defined undercut margins over all pressure points. A bed-sore on the left hip measured 12 cm. in diameter. Well-marked rheumatoid deformities were present in both hands and feet. The finger-nails were soft, swollen, and greyish.

Joints: Thickened, fibrous synovia were present in both *right knee* and *hip joints*. The cartilage over most of the articular surfaces of the knee was eroded, and the suprapatellar synovial pouch had been obliterated. There was osteoarthritic ridging of the patella. Sections through metacarpophalangeal and interphalangeal joints (Figs. 5 and 6) showed varying degrees of damage due to "burn-out" rheumatoid arthritis. There was fibro-vascular pannus opposite the joint space; this had extended over and replaced the peripheral articular cartilage. In places the fibrous pannus extended into the marrow spaces of the neighbouring bone: fibrous adhesions were present. No lymphoid foci were seen in the synovium. The bones generally had thin cortices and soft cancellous tissue. The vertebrae showed a moderate degree of osteoporosis (Fig. 7).

The *tongue* had smooth edges with a papillated centre. The *oesophagus* was normal. The *stomach* was small, but the body of the stomach was not obviously atrophic though the mucosal folds were scanty and small. A shallow ulcer with sharp edges, 1.2 cm. in diameter, was present on the lesser curve just proximal to the pylorus. Microscopically, oxyntic cells were fairly easily found in an otherwise rather autolysed mucosa (Fig. 8). There was no inflammatory infiltration. Patches of intestinal metaplasia with Paneth cells were present. The *small intestine* was normal. The ghosts of elongated, tenuous villi were clearly seen and there was no thickening of the basal part of the mucosa. The *large intestine* was normal, apart from a finely granular serosal surface over the transverse colon. This was associated with fine fibrous adhesions all over the upper peritoneal cavity and involving the liver and *spleen*. Trapped in these fibrous adhesions were a number of clear, yellow fluid blebs, up to 2 cm. in diameter. Externally there was a suggestion of granularity on the surface of the *liver*, 1,560 g. (normal 1,400 g.). The cut surface showed pale yellow-white widening of the portal tracts and a preservation of lobular architecture. Microscopically there was a patchy increase of fibrous tissue in the portal

tracts with a perilobular distribution. No regenerating nodules and no cirrhosis were seen. There were no *bile-duct* proliferations. The *gall-bladder* and *biliary system* were normal. The *pancreas* was normal.

Both *pleural spaces* were obliterated by dense fibrous adhesions. In view of the absence of chronic lung disease, these adhesions, as well as those in the other serous membranes, were probably the result of a rheumatoid serositis. The *larynx* was normal. The *trachea* and *main bronchi* were inflamed, with a purulent bronchiolitis. The *right lung* weighed 680 g. (normal 400 g.) and the *left lung* 595 g. (normal 320 g.). They were the seat of a bronchopneumonic consolidation especially in the upper lobes. Several small abscesses, up to 2 cm. in diameter, had formed. Microscopic examination confirmed the bronchopneumonia and the acute abscess formation.

The *pericardial space* was obliterated by fine fibrous adhesions. The *heart* weighed 255 g. (normal 330 g.). The chambers were of normal thickness and the valvular orifices were normal. The cusps of the mitral valve were normal for her age. Chordae tendineae were normal. The coronaries contained only a few plaques of atheroma in widely patent vessels. *Microscopically* the muscle fibres of the myocardium appeared healthy. There were a few miliary abscesses in the myocardium (Fig. 9). The mitral valve showed slight fibrous thickening. The *aorta* showed confluent atheroma without ulceration in both thoracic and abdominal portions. A nodule (0.8 cm. diameter) was found attached to the wall of a small artery (0.2 cm. diameter) behind the right lobe of the *thyroid*. On microscopic examination this was a small saccular aneurysm, filled with laminated thrombus and with a fibrous-tissue wall. The internal elastic lamina ended abruptly at the neck of the sac.

The capsules stripped easily from both *kidneys* (right weighed 135 g., the left 115 g.: normal 155 g.), which had finely pitted surfaces due to mild ischaemic disease. The corticomedullary pattern was normal. Microscopically the only abnormality was focal ischaemic scarring with an occasional hyaline glomerulus. Normal *ureters* and *bladder*. A serous cyst, 2 cm. in diameter, was present in the right ovary. A pedunculated subserous fibromyoma, 4 cm. in diameter, was attached to the lower part of the left lateral wall of the uterus. Microscopic examination showed a normal postmenopausal endometrium.

The *spleen* was grossly enlarged, weighing 765 g. (normal 150 g.), with a thick fibrous capsule. The parenchyma was uniformly red-brown without visible Malpighian follicles. No amyloid was present. Microscopic examination showed a hyperplasia of the reticulo-endothelial cells of the pulp and an atrophy of the lymphoid tissue. No iron was detected by Perl's test. There was normal red *marrow* in vertebrae and sternum. In the femur red marrow extended down to about the middle of the shaft, mixed with patches of gelatinous adipose tissue. Histological examination of the marrow showed an increase of primitive cells of the leucopoietic series, chiefly promyelocytes. The mesenteric and abdominal para-aortic *lymph nodes* were enlarged up to 2 cm. in diameter, with a fleshy, pinkish cut surface. Microscopically they showed a mild reactive hyperplasia.

The *pituitary* was normal. Histological examination showed a moderate degree of Crooke's hyaline change as a result of cortisone administration. The *thyroid* weighed 20 g. and contained a few small colloid "adenomata," one of which contained brown sludge-like material. Microscopic examination confirmed the presence of colloid nodules, and showed a few miliary abscesses and a small focus of adipose and osseous metaplasia. The adrenals were small (right 5 g., left 4 g., normal 5 to 7 g.). They had a very narrow, lipoid-depleted cortex and a relatively prominent medulla. Microscopy confirmed these findings.

The *brain* weighed 1,455 g. (normal 1,300 g.). The cerebrum and brain stem were normal, as were also the circle of Willis and the venous sinuses. Section of the iris showed no residual evidence of iritis. Section of lacrimal gland showed a mild chronic inflammatory infiltrate.

Pathologist's Diagnosis

(1) Rheumatoid arthritis. Osteoporosis.

(2) Pernicious anaemia (treated).

(3) Hepatic fibrosis.

(4) Bed-sores; terminal bronchopneumonia with abscess formation.

(5) Crooke's hyaline change in pituitary and adrenocortical atrophy.

(6) Splenomegaly (? due to rheumatoid disease).

Discussion

Dr. Dixon: Two of the fingers were removed after death and cut in sagittal section at Taplow (Fig. 4).

There are a lot of points for discussion, but two seem especially interesting. One is the discrepancy between the pathologist's findings of "burnt-out" rheumatoid arthritis, and our findings of an active disease process examplified by a very high sedimentation rate despite steroid therapy. The second is the high plasma-protein concentration which is apparently present despite the absence of lymph follicles and of plasmacytosis in the synovia of the joints that were examined. One other point on which I would like to hear something from the experts here is whether there is any relationship between pernicious anaemia and the so-called auto-immune diseases, if we can include rheumatoid arthritis and disseminated lupus under that heading for this purpose. There has been some work on whether the destruction of the gastric lining in pernicious anaemia might not be the result of an auto-immune reaction. I don't know any more about this, perhaps the haematologists can enlighten me. Perhaps I could ask them to discuss these two points: whether or not there is any relationship between pernicious anaemia and rheumatoid arthritis, and why this patient should have such a high level of gamma-globulins when there are so few of the cells which we normally think of as the gamma-globulin-forming cells.

Periportal Fibrosis and Splenomegaly

Professor J. McMichael: Before we embark on this problem one or two features must be disposed of. For example, this little bit of periportal fibrosis in the liver is unconvincing. I don't think we can call this cirrhosis.

Dr. Azzopardi: Oh, definitely not, but there *is* a portal fibrosis. It's not normal.

Professor McMichael: It doesn't link to any known disease and it looks more like a pig's liver.

Dr. Azzopardi: Well, it is a disease in that it is abnormal. I mean you cannot laugh it off, there's a definite abnormality there.

Professor McMichael: I'm not laughing it off. . . . Then the big spleen, I would like to ask Dr. Dixon if, with rheumatoid arthritis, we can call this Felty's syndrome and start discussion from that point.

Dr. Dixon: Well, Felty described various patients with a big spleen and rheumatoid arthritis. He probably included a variety of causes of big spleen amongst his original patients, but the syndrome as we now understand it is the triad of rheumatoid arthritis, a large spleen, and leucopenia—which she didn't have.

Dr. Azzopardi: Did she ever have a leucocytosis when she had the terminal infection, because there was a lot of sepsis there?

Marrow Promyelocytes

Dr. Dixon: We may be able to shed a little light on those funny cells in the marrow. During her terminal admission she was in fact treated for her iron-deficiency anaemia, but she was not given cyanocobalamin injections until the last week or so, so that she may have been in a relatively early state of B_{12} depletion.

Dr. Azzopardi: The haematologists apparently thought that they were early myeloid cells and that they were mainly promyelocytes but that there was some maturation defect.

Dr. J. C. White: Yes, there is a certain amount of difficulty in establishing the nature of these cells. On the other hand, of course, if there is a lack of haemopoietic factor, in the first stage, I wouldn't say that they would be proliferated. I would say that the nuclei became larger and the chromatin more diffusely staining rather like these cells, but I shouldn't have thought they would have become too prominent in numbers.

Nature of Anaemia

Professor McMichael: Yes, Dr. White, can you answer some of the questions of Dr. Dixon's about the anaemia? She was studied at University College Hospital, where macrocytic anaemia was not at first recognized. Yet she had it later.

Dr. White: Well, it would appear that it was well established that the bone marrow in 1954 was megaloblastic and the red cells macrocytic, so that to that extent the diagnosis was confirmed. We ourselves never saw any evidence, I'm afraid, of the pernicious anaemia, because she had been treated with cyanocobalamin and vitamin B_{12}. What we did see was the evidence of iron-deficiency anaemia which one would associate much more commonly with rheumatoid arthritis. This is not surprising in view of the medication with codeine compound and there was also a small single gastric ulcer.

Professor McMichael: A small gastric ulcer?

Dr. Dixon: A small prepyloric gastric ulcer.

Professor McMichael: That is very unusual in anybody with pernicious anaemia, isn't it?

Dr. White: Yes.

Dr. Azzopardi: Well, in this case there were all these oxyntic cells still there. The average case of pernicious anaemia, especially at the time of death, does show a completely atrophic stomach wall, not only the mucosa but the muscularis as well. The whole wall is thin, paper thin, and the oxyntic cells have usually disappeared by the time the patient dies, so this case was unusual in that respect.

Professor McMichael: In short, this is a woman with macrocytic anaemia and a stomach that doesn't fit in with pernicious anaemia.

Dr. Azzopardi: Well, yes. It's not very typical, but there have been genuine cases of pernicious anaemia, with a good family history described, who still had oxyntic cells in the stomach.

Professor McMichael: You say you very seldom see them at necropsy.

Dr. Azzopardi: At necropsy they are rarely seen. It is unusual.

Gastric Atrophy and Auto-immunity

Professor McMichael: Let us get an answer on whether or not this gastric atrophy is due to an auto-immune process and whether this has any relation to rheumatoid arthritis.

Dr. Azzopardi: Well, this has been suggested, mainly as a result of the histological appearances of the gastric biopsies. Study of these has shown that inflammatory infiltration can be found in the mucosa in the early stages, and it has been suggested that this inflammatory process, in the early stage, could be a reaction to some antigenic constituent of the gastric cells, and that, as the process goes on, these cells are knocked out, so to speak, and there is finally the picture of gastric mucosal atrophy without inflammatory cells. The idea is that what we were seeing in the old days was the end-stage of atrophy following inflammation—this is just a theory. Not everybody holds with this.

Dr. White: But in this case there is a well-marked family distribution, and the view that pernicious anaemia is genetically determined is now held widely.

Dr. Dixon: I don't see why that should be against it. There is a well-marked family history in a number of the diseases which we call auto-immune.

Professor McMichael: I think we should make it clear to the students that this is sheer speculation. We are casting round for new ideas to explain some of the things we don't understand. Auto-immune disease is speculative and no more substantiated than the old "toxins" postulated to explain everything in the early part of this century.

Was Osteomalacia Excluded?

Dr. M. D. Milne: Regarding the pernicious anaemia, so far as I can see, this diagnosis was never subjected to the scrutiny and severe criteria which modern haematologists demand. That is the demonstration of malabsorption of vitamin B_{12}, correctable by oral intrinsic factor. Could I ask just a further point in relation to the high phosphatase which I don't think has been explained? Can the pathologists assure me that there was no histological evidence of osteomalacia in these bones, because a combination of macrocytic anaemia, which might not be pernicious anaemia, and skeletal lesions, and a high phosphatase, makes you highly suspicious of osteomalacia as well as osteoporosis, and I have seen no evidence to show that this was not present.

Dr. Azzopardi: Well, I looked for osteoid seams and didn't find any, especially after I saw the high alkaline phosphatase last night. You are obviously thinking of an idiopathic steatorrhoea which would explain both, but in fact we looked at the jejunum, and although it

shows marked autolysis you can see perfectly beautiful, normal, long, thin villi, and there is not the slightest sign of idiopathic steatorrhoea.

Dr. Milne: Could we have details of the histological technique by which you excluded osteoid seams over the bony trabeculae?

Dr. Azzopardi: Oh, that was admittedly only a haematoxylin-eosin preparation.

Dr. Milne: But surely that is a very inferior and inconclusive technique?

Dr. Azzopardi: It is, yes, but the histology of the intestine excludes idiopathic steatorrhoea.

Dr. White: Another point with regard to the phosphatase. The macrocytic anaemia of this patient was well controlled with cytamen containing vitamin B_{12}, and I should have thought that for response in the other case folic acid would have been more likely to be needed.

Dr. Milne: According to Dr. Mollin's work, they seem to find a deficiency of B_{12} in malabsorption syndromes as often as a folic-acid deficiency, and sometimes a deficiency of both factors. I have seen full correction by B_{12} alone in some of these cases.

Anabolic Steroids for Backache

Professor McMichael: There are lots of other things we have to discuss: treatment of backache by testosterone and oestradiol. That sounds a most odd mixture. Can you give us an explanation of this; what does it do?

Dr. Dixon: It was given originally in an attempt to reverse the calcium loss and nitrogen loss in these people with osteoporosis, and we have found empirically that anabolic steroids, of which this combination is one example, can relieve the pain of a crush fracture secondary to osteoporosis. I don't know any good evidence that these drugs will reverse the osteoporosis itself in a long-term treatment, but we do seem to be able to relieve pain within a week with them in most cases, and as such they are quite valuable.

Professor McMichael: Testosterone to promote nitrogen retention and oestradiol to give calcium retention?

Dr. Dixon: No, both of them have the same effect on nitrogen retention, but the idea is that the secondary sexual effects are different and you need less of each.

High Gamma Globulin

Professor McMichael: In the last stages she had a very severe infection. This can account for gamma-globulin elevation, and you also see this with rheumatoid arthritis?

Dr. Dixon: Yes, sir, you do, but you normally get it in the active cases where you can usually demonstrate a great deal of plasma-cell infiltration in the joints. Such patients often have some enlargement of lymph nodes, and I was just struck by the fact that in this patient the plasma cells and lymph cells seemed to be very scarce.

Dr. White: They certainly were present in the bone marrow and appeared to be quite actively producing protein.

Dr. Dixon: Perhaps that is the answer.

Dr. White: Isn't this unusually high, the gamma-globulin?

Dr. Dixon: It is unusually high, yes; however, the electrophoretic strip was not indicative of myeloma.

Dr. White: No, there was no suggestion of myeloma.

Dr. Azzopardi: What do you think of the splenomegaly, Dr. Dixon? Would you accept that as part of the rheumatoid process?

Dr. Dixon: Well, this is really back to the question of Felty's syndrome. Moderate degrees of splenic enlargement we do see from time to time, from just palpable to one or two fingers breadth enlarged in chronic rheumatoid arthritis. I can tell you no more than that.

Dr. Azzopardi: Do cases of Felty's syndrome generally have a high gamma-globulin?

Dr. Dixon: Usually, yes.

Dr. Azzopardi: So really they all go together, don't they—the big spleen, the high gamma-globulin, and abnormal liver function tests? In this case it's really a question of explaining the whole triad.

Dr. Dixon: Well, that is a very empirical selection of the many features here.

"Liver-function" Tests

Professor McMichael: I don't think "liver-function" tests are really specific to the liver. You can get plasma-protein changes in rheumatoid arthritis, you can get phosphatase changes with various bone and endocrine disorders, and there is nothing about these estimations specific to the liver. You mustn't assume that the liver was abnormal.

Professor E. J. King: What about the high zinc and thymol turbidity tests?

Professor McMichael: Is that specific to liver disease and not seen in any other disturbance?

Dr. Azzopardi: They are abnormal in Hashimoto's disease which gives a false-positive result.

Professor McMichael: There is no test specific to the liver. Now this patient obviously developed infection while on steroid treatment, and this creates an immense problem.

Systemic Lupus Erythematosus

Dr. Azzopardi: In retrospect, Dr. Dixon, what do you think was the illness she had in 1954? Do you think it was rheumatoid disease, or systemic lupus erythematosus which has cleared up and left no evidence, or was this some other disease with an unknown name?

Dr. Dixon: We see patients with rheumatoid arthritis who develop symptoms in parts of their body other than their joints, and when this condition becomes severe we call it malignant rheumatoid arthritis. Such patients often show a polyserositis, including pericarditis. Pericarditis is probably more common than we realize, because we cannot be listening to our patients all the time. It is certainly a common finding at necropsy. Fever of moderate degree is also common in these people, and usually some degree of mood or mental change. Where all this stops being malignant rheumatoid and starts being disseminated lupus, I don't think you or I or anyone can tell. At the moment I would say this is all consistent with severe rheumatoid arthritis.

Dr. Milne: Dr. Dixon made a statement that all cases of lupus erythematosus have this antinuclear

factor. Could he tell us how he defines a group which includes all cases of lupus erythematosus without reference to the antinuclear factor? You have got to have some separate standard reference to say that all cases of lupus erythematosus have this factor.

Dr. Dixon: I would like to correct Dr. Milne. I said almost all, and I am referring to the work of Holborow at Taplow. The basis of this is the clinical diagnosis, which I think it must be in all these attempts to relate a pathological feature with a clinical feature.

Relationship to Lupus Erythematosus

Dr. P. Hugh-Jones: I think the relationship between diffuse lupus erythematosus and rheumatoid arthritis is an extremely obscure one, to say the least of it. We had a patient, whom Dr. Dixon saw for us, who had had a typical lupus erythematosus rash on the face many years ago, and who had a leucopenia but never had any lupus erythematosus cells in her serum on repeated tests. She was treated with steroids, but these were stopped because of a purpuric rash. As soon as they were stopped she developed rheumatoid symptoms for the first time, and then her differential agglutination test became positive. When she was put back on steroids it became negative and her rheumatoid arthritis apparently disappeared. Our patient had Sjögren's syndrome as solely a manifestation of lupus erythematosus. Had your patient any signs of Sjögren's syndrome?

Dr. Dixon: In general, no great advantage is served by trying to confuse the two diagnostic pictures, but we do have to remember that these intermediate cases do occur. I would pick you up on one point. This patient did show some evidence of Sjögren's syndrome; it is fairly common in severe rheumatoid arthritis. She had this dry mouth, she also had a history of inflamed eyes, and it wouldn't be the first time that severe inflammation of the eyes, due to kerato-conjunctivitis sicca, had been diagnosed as iritis; she also had some degree of chronic inflammatory change in the lacrimal glands at death.

Dr. Azzopardi: I found evidence of that.

Gold Treatment

Professor McMichael: Can I mention the gold treatment, just as a possible explanation for any minimal liver damage? This treatment used to be associated with jaundice when it was being widely given for rheumatoid arthritis, and we don't know whether this was a syringe-borne infective jaundice or whether gold really damages the liver.

Dr. Dixon: I cannot answer it. I've never seen jaundice complicating gold treatment, probably because gold treatment has not been used nearly as commonly in the last few years as it once was, when it was about the only method of treatment available.

Professor McMichael: I was horrified to hear that gold might be coming back into use, for it damages the kidneys as well.

Dr. Dixon: Recently a carefully controlled clinical trial, with a follow-up extending over three years, has shown that patients on gold treatment have done better during that three years than patients receiving injections containing only homoeopathic amounts of gold. Of course, gold is a lot safer now that we have got steroids and B.A.L. (dimercaprol): if it was justified then, it is perhaps a little more justified now.

Professor McMichael: In spite of severe crippling, disabling rheumatoid arthritis, complicated by infection, she didn't show any amyloid change.

Dr. Azzopardi: No, she didn't.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to Mr. W. W. Brackenbury for the photographs.

CLINICAL PATHOLOGY AND BIOCHEMISTRY

The Association of Clinical Pathologists held its 67th General Meeting from September 21 to 23 at the Royal College of Surgeons. The meeting included Dr. G. Stewart Smith's presidential address on "Clinical Pathology and Forensic Medicine," two symposia ("Manpower Economy in the Laboratory" and "Some Aspects of Modern Sterilization"), and on the last day a joint meeting with the Association of Clinical Biochemists. Below we print abstracts of some of the papers.

Metabolism of the Obese

G. L. S. Pawan said that in the obese daily calorie intake was sometimes no greater, and might even be less, than that of non-obese persons. Total energy expenditure, efficiency of energy utilization, and the response to calorie reduction might differ from that in normal individuals. Fasting blood levels of non-esterified fatty acids and pyruvic, lactic, and citric acids were higher than normal, and responded differently to glucose administration. Normal persons given a 1,000-calorie diet, in which 90% of the calories were supplied as fat, exhibited within a few days marked hyperketonaemia, hyperketonuria, hypoglycaemia, and a marked negative nitrogen-balance. The obese seemed to tolerate this diet better than the non-obese, showed little or no ketosis, maintained their blood sugar within normal levels, and suffered little loss of body protein. In the obese, there was some evidence of increased use of the pentose phosphate pathway of carbohydrate metabolism; liver function was often abnormal; and the phosphorylase activity of subcutaneous adipose tissue and the urinary excretion of certain steroids were higher than in normal persons. He suggested that in the study of obesity attention should be directed not only to regulation of appetite and calorie-intake but also to the expenditure of energy and to the metabolic factors influencing synthesis, mobilization, and utilization of the body's stores of fat.

Biochemical Changes After Partial Hepatectomy

H. Cleave had studied post-operatively three of Mr. Rodney Smith's cases of partial hepatectomy. The estimated bulk of liver tissue removed was 75% in Case 1, 90% in Case 2, and 50% in Case 3. In Case 2 the blood urea fell from its pre-operative level of 23 mg./100 ml. to 9 mg. on the second day, and the prothrombin level fell from 466 mg./100 ml. to 266 mg. on the first day, but rose to 692 mg. on the ninth day. These findings suggested that removal of nine-tenths of the liver was near to the limits of tolerance. Of the serum enzymes studied, the glutamyl pyruvic transaminase showed a rapid rise in the first three days in all cases, reverting to normal over a varying period up to 20 days. This was assumed to reflect the necrosis of some of the residual tissue. The lactic dehydrogenase, on the other hand, rose after operation and maintained a fluctuating high level for 14 days. Experimental studies suggested that this might represent the initial stages of liver rejuvenation. The albumin levels showed an immediate post-operative fall with a corresponding rise in total

globulins, and were recovering only slowly during the patient's stay in hospital. In all three patients the histological appearance of the residual liver was normal.

Muscle Biopsy in Alimentary Disorders

C. T. G. FLEAR, A. O. CAMPANA, and IRENÉ FLORENCE said the potassium contents of small samples of skeletal muscle could be estimated in a few hours. Technically, therefore, it should be possible to make clinical use of muscle biopsies, which would be an advantage in view of the unreliability of serum levels as indices of body and cellular content. On the face of it this should not be difficult, as the cell potassium provided about 99% of the potassium in a sample. Difficulties arose, however, in the choice of suitable standards for evaluating specimens. In spite of the very considerable variability in composition of human skeletal muscle, a biopsy could afford a useful index of cellular potassium throughout the muscle sampled. But it was essential to take into account its sodium content, and it was also necessary to evaluate a biopsy against normal values obtained from the same skeletal muscle. The authors discussed the interpretation of their findings from patients with various alimentary disorders.

Fragility of Leucocytes

H. G. H. RICHARDS and D. L. RICHARDS first described their technique for estimating the osmotic fragility of leucocytes, which they had applied to 17 cases of leucopenia, covering a wide variety of causes from toxic to myeloproliferative. In 14 of the cases the fragility was very markedly increased, while in three it was significantly decreased below normal. They suggested that the osmotic fragility of leucocytes was a measure of their average length of life.

Red-cell Antigens and Enzymes After Low-temperature Storage

R. G. HUNTSMAN, B. A. L. HURN, ELIZABETH W. IKIN, H. LEHMANN, and J. LIDDELL said that the rapid freezing of red cells in liquid nitrogen was a convenient alternative to preserving them with glycerol for serological purposes. Anticoagulated blood, mixed with half its volume of 40% sucrose, was added drop by drop to liquid nitrogen through a fine needle. The frozen pellets were then stored in a Linde liquid-nitrogen refrigerator, which cost about £200 to buy and 8d. a day to run. Recovery of intact cells, grouping properties, and four intracellular enzymes had been measured after storage at −196° C. (liquid nitrogen), −100° C. (electrical refrigerator), and −78° C. (carbon-dioxide snow). Over a period of two months at −196° C. recovery remained at 90–95%, which was the same as obtained immediately after freezing. There was no deterioration in grouping properties. Aldolase and glutamic oxalacetic transaminase had fallen by 14% and 17% respectively. Glucose-6-phosphate and 6-phosphogluconic acid dehydrogenase activities appeared to be enhanced. Present results suggested that storage at −100° C. and −78° C. was less satisfactory.

Rapid Heparin-tolerance Test

R. D. EASTHAM said that the plasma recalcified clotting test had been modified to reduce the normal time from the quoted range of 90–180 seconds to 34–45 seconds, and this had greatly improved reproducibility. This improved test had then been used as a basis for a heparin-tolerance test. Two concentrations of heparin were used such that the final heparin concentrations in the reacting mixtures were less than those which would interfere with either the thrombin–fibrinogen reaction or the action of formed thromboplastin. The improved plasma calcium clotting test and its modification as a heparin-tolerance test had been used in an attempt to detect either those cases particularly liable to develop post-operative thrombosis or those which had very recently developed thrombosis. Preliminary results showed that there was a definite shortening in the clotting times, both with and without added heparin, after operation. Blood from patients treated with phenylindandione gave times prolonged above normal, and these results showed only rough direct correlation with either the Quick one-stage prothrombin time or the thrombotest results.

Fibrinolysis Related to Age in Men

H. T. SWAN had assayed fibrinolysis by the time taken for sterile plasma clots to lyse at 37° C. Three different patterns of results had been obtained and this had prevented easy comparison of experiments. Most comparable results were obtained by noting the lysis-time taken by the 50% plasma clot. All the results were based on this figure alone. Assays had been performed on 192 men whose ages ranged from 21 to 87 years and who were at the time in surgical and radiotherapy wards. Days of stress were avoided as far as these could be recognized. Blood was drawn about 10 a.m. by the same person using an identical technique. The mean age within each decade was calculated, together with the mean lysis-time of the same group of patients. When these values were plotted against each other it became obvious that there was a faster rate of lysis with increasing years. The slope was sufficiently obvious not to require significance testing. By the method used, the lysis time at the age of 40 was approximately halved by the age of 80. The results for cases grouped because of known malignancy were identical to those where no malignancy was recognized and for the group as a whole.

ABO and Rhesus Groups in Perthes's Disease

J. M. CAMERON and MARIAN M. IZATT had determined the ABO blood groups and Rhesus phenotypes of 142 children from a series of 185 suffering from unequivocal Perthes's disease. Where possible their parents and sibs were also grouped. The results showed no apparent relationship between the development of Perthes's disease and the distribution of the ABO groups in the children concerned. There was a suggestion, however, of an increase in the incidence of the Rhesus-negative phenotype, rr (cde/cde), among the affected children. Parental and sibship studies showed that an association—if one did exist—was unlikely to be due to genetic stratification within the population. Sera from the mothers of affected children were examined for the occurrence of Rhesus antibodies. The conclusion was reached that maternal antibody, acting through the agency of haemolytic disease of the newborn, played no appreciable part in the aetiology of a subsequently developing Perthes's disease in the child.

Monoamine Oxidase Activity in Toxaemia of Pregnancy

M. SANDLER, JENNIFER COVENEY, and ELIZABETH BALDOCK said they had detected a small but significant decrease in monoamine oxidase activity in placentas from patients with toxaemia of pregnancy compared with those from normal pregnant subjects. This change tended to be greater in patients with more severe manifestations of the disease. Although the recovery of 5-hydroxyindoleacetic acid after 5-hydroxytryptamine ingestion was significantly decreased in toxaemia, suggesting the possibility of a generalized monoamine oxidase defect, this interpretation was not confirmed when 24-hour excretion of tryptamine was used as an index of enzyme inhibition. There was a significant increase in tryptamine output in normal pregnancy, but, instead of the further increase which might have been predicted in the presence of a generalized enzyme defect, toxaemic patients showed a decrease to non-pregnant levels.

Cerebral Oedema and Minor Burns

J. L. EMERY and C. CAMPBELL-REID described six children between the ages of 3 and 13 months who had developed cerebral symptoms within two to eight days of a relatively minor burn. All six children had died with gross swelling

of the brain and pressure cones. One child who had similar symptoms but did not die later developed a spastic hemiplegia. The authors also described the technique by which such cases could be diagnosed at necropsy by approaching the foramen magnum from the back of the neck.

MEDICAL SCHOOL OPENINGS

WESTMINSTER MEDICAL SCHOOL

The rapidly changing face of modern medicine, and the subsequent effect on the student to-day, provided the theme of the inaugural address by Sir Eric Ashby to the Westminster Medical School on October 2. Every community and society, he explained, however primitive, to-day and in the past, had some form of education, and even lowly African tribes had their own form of "medical examinations." But throughout every pattern of education there was always woven one assumption: that each generation would, by and large, live amid the conditions governing the lives of its forefathers, and would in turn pass its knowledge on to their children. This assumption lay at the root of our own educational system. However, that assumption was no longer valid.

Unprecedented Tempo of Change

It was difficult for us to grasp just how slowly ideas had changed in history. For thousands of years there had been no fundamental change in man's concepts of the sun and the planets, and scarcely one major invention in technology; from the dawn of history to only about 84 years ago no one had established beyond dispute that infectious diseases in man were due to living organisms. In fact, the student had always been able to assume that what he learned would last him for the rest of his life. But now we were living in the first period of history for which this assumption was false, and very much of the experience of one generation now was quite irrelevant to the next. Some of what the student learned to-day would become obsolete in a few years, not only in medicine, but in diplomacy and economics.

It was therefore essential for every professional man, particularly in medicine, to have frequent opportunities for re-education, continued Sir Eric, and medical schools were making every effort to meet those needs.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL

Lord Taylor of Harlow took as his theme for the inaugural address to St. George's Hospital Medical School, on September 29, "The Student of Medicine." He said that to be a good student of medicine it was necessary to feel the romance of the subject, the thrill of learning new things, and learning to use one's hands, eyes, ears, and brains to serve other human beings.

Student's Tasks

The student's first job was to get through his examinations, and the second to become a good doctor. These did not necessarily provide the same problem, as a statistical examination of final examinations showed that the same questions appeared regularly—40% of the questions were about orthopaedics; in the final clinical examination, for instance, the student was unlikely, for obvious reasons, to be confronted with an acutely ill or dying patient. Lord Taylor suggested that the student should have a plan for examinations. Exercises in how to tackle examinations intelligently would also teach something more; it would mean learning how to tackle medicine intelligently, instead of like a walking computer. Medical examinations were the envy of other faculties, because they were designed to find

(*Continued at foot of next column*)

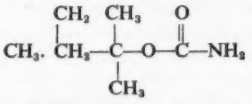
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Emylcamate

"Striatran" (Merck Sharp and Dohme).

Chemistry.—This drug is 1-ethyl-1-methylpropyl carbamate and has the following structural formula:



Pharmacology.—A number of tertiary alcohols were screened by comparing their effects on animals with meprobamate. Emylcamate proved the most effective in the following respects: allaying artificially produced restlessness in mice; antagonizing strychnine; suppressing chemically and electrically induced convulsions; and in producing a rapid flaccid paralysis in rabbits with considerably less than a lethal dose. It is possible that the drug acts by blocking transmission of impulses through internuncial circuits.

Therapy.—This drug has been recommended principally for anxiety and tension, as it is assumed that there is a parallelism between muscle relaxation and the relief of these symptoms. A suitable dosage is 200 mg. three or four times a day. Information on therapeutic results is meagre. It was used to relieve the neurotic symptoms of 60 patients who had been alcoholics, and was found to be superior to meprobamate in this respect. In another study the drug was given to patients with a heterogeneous group of conditions, most of them painful, but so diverse as to include stuttering, pruritus, threatened miscarriage, melancholia, and irritability; 85% of these patients are reported as "improved."

The drug has been carefully appraised for "behaviour toxicity" (i.e., its effect on motor performance, perception, and judgment as used in such tasks as driving) by means of specially contrived tests. In single doses of 400 mg. it had no measurable effect, but 800 mg. slowed reaction time. It produced a feeling of "calmness" in subjects working in the discomfort of extreme confinement without affecting the quality of their performance. In short, there is evidence that mental distress is transiently relieved by replacement with euphoria.

Side-effects.—These are infrequent; drowsiness is most common. In a small number of cases nausea, dizziness, and transient eosinophilia have occurred.

N.H.S. Basic Price.—100 tabs., 25s. 6d.

(*Continued from preceding column*)

out if the student was fit to be turned loose on the public and practise as a doctor, and they managed to do that very well.

There were certain occupational risks in the medical profession, and if students knew them they could easily avoid them. The first was pomposity. The next one was intellectual sloppiness; that battle had to be fought and won in one's student days. The third was "money grubbing." Nobody should grumble about money, but should get on with life and improve it. All students to-day had better opportunities than were ever enjoyed by their predecessors. The last risk was "staying put." It was wrong to play for safety by staying on at medical school too long. To-day there were jobs all over the world and in all parts of Britain. Young people should travel before settling down, and drop in whenever possible to see new doctors and hospitals. Medicine knew no boundaries.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Christmas Gifts Fund

Sir,—I should be grateful if you would allow me space to make the customary annual appeal to enable the Royal Medical Benevolent Fund to send a Christmas gift to each of the Fund's regular beneficiaries. The Fund does remarkably good work by providing grants and annuities to those members of our profession and their near relatives whom misfortune has rendered unable to provide for themselves, but this does not allow for any extra expenditure at Christmas. That is why this special appeal is made.

The medical profession is generous-minded and I am sure that it will only need this reminder to ensure a liberal response sufficient to gladden the hearts of our beneficiaries this Christmas. Would donors kindly send their contributions, marked "Christmas Gifts," to the Royal Medical Benevolent Fund, 37 St. George's Road, Wimbledon, London S.W.19.—I am, etc.,

Zachary Cope,
President,
Royal Medical Benevolent Fund.

London S.W.19.

Geriatric Services

Sir,—The letter of Dr. Peter R. T. Wood (September 30, p. 893) brings up a subject which, I am sure many G.P.s will agree, is extremely important. He calls attention to a situation which is indeed in many areas a desperate one. The problem of giving even elementary attention to the increasing number of lonely elderly patients is threatening to cause the breakdown of some practices by increasing the daily amount of work to be done to impossible degrees—apart from the frustration and anxiety of knowing that the old people under one's care are not getting the help that they should.

In most areas the geriatric services do their best with pathetic numbers of beds at their disposal in both hospitals and welfare homes. In this practice alone many examples could be given of really serious problems occurring daily. For example, the elderly lady with Parkinson's disease who lives alone and who is being taken daily to the geriatric unit for exercises, but who falls frequently and lies alone until someone happens to find her. With her it is simply a question as to whether a fatal fall or a welfare home vacancy will occur first. Welfare officers say that the waiting-list for homes is so long they are ceasing to add new names to it at present. I do not mean that hospitals or welfare homes are the answer in all cases, but a great deal more help is needed to sort out the problem.

The ancillary services (home-help organizers, health visitors, voluntary organizations, etc.) do what they can with a hopeless task, but it is the G.P.s who are responsible for their old people, and who have to try and organize help. Daily and weekly the difficulty increases as the average age of the population also increases, and I claim that the matter is urgent.—I am, etc.,

Vera E. Claxton.

Hove 3.

Routine Immunization

Sir,—A decade or two ago when a young child suffered one of his many injuries in or around his home mother treated the wound or if it was beyond her skill took the child to her doctor. If the injury required hospital treatment the doctor arranged it. This admirable practice has changed. Little people now frequently walk into casualty departments without even telling mother. Many doctors when told of an injury advise the mother to take her child immediately to hospital. And so the former intimate liaison between the general practitioner and the hospital service is lost.

Repercussions from this modern practice can be grave. Recently we received a 5-year-old boy accompanied by his older sister. The child had cut his knee playing in the garden. The child and his sister were asked if the boy had been immunized against tetanus. They did not know. After the wound had received the appropriate local treatment the boy was given a test dose of antitetanic serum without reaction, then 750 units was administered. On his journey home he became unconscious and was returned to hospital in a grave collapsed state, typical of anaphylactic shock. Happily he recovered.

Subsequently I received a letter from his doctor and learned that he had previously actively immunized this child against tetanus. Had we known this, the child would have received a booster dose of toxoid and would have escaped a complication that endangered his life. This is an everyday dilemma in casualty departments everywhere. All hospital staff are, or should be, aware of the danger of anaphylactic shock following injections of horse serum; all would welcome a change from antitetanic serum to the safe booster dose of toxoid when the risk of tetanus is real. Most casualty officers know that the test dose of antitetanic serum is not reliable.

How then can hospital staffs know when injured young people have been actively immunized? Little people now come to casualty departments in considerable numbers and unaccompanied by any adult. Generally they do not even know the name of their doctor. We were criticized in this particular case because we did not take the precaution to ring the doctor up or get into contact with the child's mother. Yet it would be a considerable burden on the police service if we asked them always to contact the parents of these children, and on the hospital to hold these patients until this information was obtained.

One would advocate after active immunization a small tattoo-mark, no bigger than a pin's head, behind the lobe of the right ear, but without consent this is illegal, an "assault on the person." Yet what is to happen to our little patient when next he falls in the garden and cuts his knee? Will a new house-surgeon recognize him, or another hospital know of his previous grave horse-serum reaction? The answer to this and similar problems is surely the routine immunization against infectious diseases (including tetanus), as advocated in a recent memorandum to all general practitioners and medical officers by the Ministry of Health (September 16, p. 763). If this routine is obligatory instead of permissive it would mark a considerable advance in preventive medicine.—I am, etc.,

William Gissane.

University of Birmingham.

SIR,—As a casualty officer I am responsible for giving antitetanus serum to thousands of patients each year. Of these a small but nevertheless definite number get local reactions, and a few a generalized urticaria. True anaphylaxis is fortunately very rare.

It is my usual practice to ask if the patient is protected against tetanus, but it is very rare to get a definite positive answer even in children. Very many, if not most, children are given triple vaccine in infancy, but when the parents are asked over 80% say, "Don't know." These children are therefore given A.T.S.

On reaching school age the diphtheria immunization is usually boosted, but rarely the tetanus. The recent Ministry of Health circular[1] (see *B.M.J.*, September 16, p. 763) makes recommendation on times for giving various immunizations in children, but does not make any suggestions on the best way of informing parents what protection has been given. I feel we need a nationally accepted scheme to provide *effective* immunization against tetanus and a reasonably foolproof method of informing the patient, or parent, that it has been done, and when the next reinforcing dose is required.—I am, etc.,

Stanmore, Middlesex. A. W. WARLTIER.

REFERENCE

[1] Ministry of Health, Circular 26/61. *Immunization in Childhood*, 1961.

Tetanus Prophylaxis and the Courts

SIR,—I wholeheartedly agree with the requests by Drs. J. Fry, H. J. Parish, and D. A. Cannon (September 9, p. 705). It is up to doctors to improve liaison between themselves, but effective personal medical record cards require much more organization as well as the co-operation of the public, and appear to be a thing of the future.

The spearhead of the authors' attack, however, is based on tetanus prophylaxis. Why is it that this disease, which kills in a year the same number of people as are killed on the roads every two days, arouses such strong feeling in the medical profession and so much writing in the medical journals? I am sure that the attitude of the courts to the omission to give antitoxin, which dates from a time when tetanus was common and antitoxin was the only means of prophylaxis, unduly influences our present approach to the problem. It is time that this attitude should be reassessed, bearing in mind the dangers and not uncommon ineffectiveness of antitoxin prophylaxis, the advantages of toxoid, the introduction of antibiotics, and the great advances made in the treatment of the disease with muscle relaxants and controlled respiration.

Only when the medical profession is no longer in fear of an outdated legal hazard will we be able to approach the problem sensibly and find a practical solution to tetanus prophylaxis, and personal medical record cards if they are still necessary, which can be applied by general practitioners and casualty officers. This is certainly not the case at present.—I am, etc.,

Fulham Hospital, London W.6. G. E. FULFORD.

Finger-tip Injuries

SIR,—Mr. F. J. Moynihan in his review of the "Long-term Results of Split-skin Grafting in Finger-tip Injuries" (September 23, p. 802) has drawn attention to the value of immediate skin cover with a Thiersch graft as the ideal primary treatment in casualty departments. The practice of training house-surgeons and students in this technique, instituted in the casualty department of Guy's Hospital by Mr. P. Clarkson, is to be commended.

It is true that these split-skin grafts, if correctly applied and retained in position with a secure dressing, will "take" well in 90% of cases and fulfil the dictum laid down by the late Sir Harold Gillies that "the best dressing for a wound is skin." What this method of treatment does not do is to restore the loss of pulp and the support which this normally gives to the nail. The deformity created by an ugly curved nail growing over the finger-end is often seen following the all-too-common injury when a child's finger is caught in a motor-car door. Quite apart from the nail deformity the loss of pulp can seriously affect the function of tactile discrimination which normally enables the finger-tip to distinguish shape, texture, and consistency. The tactile corpuscles responsible for fine discrimination depend for efficient working on the pulp being soft and elastic, and backed by a phalanx and nail to afford counter pressure. If both nail and pulp are lost this important tactile end-organ will not function efficiently.

There are therefore both cosmetic and functional grounds for restoring the digital pulp, particularly of the index finger and thumb. This can only be done either by a "flap" of skin from the palm (thenar) or the adjacent finger (cross finger), or by a thick free-graft. In young children these "flap" repairs are difficult, and for this reason I described in 1959[1] the "toe-pulp graft" in which an area of skin and pulp equivalent to that which had been lost is transferred from toe to finger to give a nicely rounded contour with support for the nail. The donor area on the toe is covered with a thin split-skin graft. The method can also be used as a secondary procedure after primary split-skin grafting in children or adults. The subsequent recovery of tactile discrimination in these toe-pulp grafts is so good that it can only be accounted for by the similarity in structure of the skin.

I would also like to endorse what Mr. Moynihan has said about "flap" repairs being outside the scope of casualty surgeons unless they have had special plastic training, and the same applies to the thicker types of free-grafts, but both these techniques have an important place in correcting deformity and the restoration of sensory function. The fact remains that a split-skin graft cannot make up loss of digital pulp and it is only by a "flap" or a thick graft that this can be restored.—I am, etc.,

Queen Mary's Hospital, Roehampton. CHARLES R. MCCASH.

REFERENCE

[1] McCash, C. R., *Brit. J. plast. Surg.*, 1959, **11**, 322.

Post-operative Pneumoperitoneum

SIR,—I was most interested in the idea suggested by Mr. Stephen Power (September 16, p. 770) of attaching an abdominal drain to a water seal. This method has already been advocated by Professor Milnes Walker.[1] Certainly it is possible for air to be sucked into the peritoneal cavity through a drain in the upper part of the abdomen, especially if this drain communicates with the subphrenic space. The main reason for this is, as stated in my paper (September 2, p. 605), that the pressure below the diaphragm is negative, reflecting that in the pleural cavity.

I feel that the main point in establishing drainage in the abdomen is for the end of the drainage tube to be related intimately to the area needing drainage—e.g., the duodenal stump or the gall-bladder bed—so that a closed compartment results. I feel it is inviting pneumoperitoneum and other complications for a drainage tube merely to be placed in the general peritoneal cavity.

Dr. Edward Thomas's letter (p. 770) is a very salutary reminder of how difficult it is to establish numerical proof in a subject such as this. The series of patients reported took over 18 months to study and collect, and it would obviously take a lifetime's work to produce series strictly comparable in all their variables. As stated, the matter cannot be considered proved, but I feel that the possible complications due to a large post-operative pneumoperitoneum would be well worth confirmatory studies by others.—I am, etc.,

Dudley Road Hospital, Birmingham 18. P. GILROY BEVAN.

REFERENCE

[1] Milnes Walker, R., in *British Surgical Practice (Surgical Progress)*, 1953, p. 215. Butterworth, London.

Extraperitoneal Fibrosis

SIR,—I feel that Mr. Stephen Power's equation of the extraperitoneal fibrosis in his case (August 19, p. 498) with the idiopathic retroperitoneal fibrosis so ably described by Raper[1] should not be allowed to pass unchallenged. The essential features of the latter disease are: (1) Insidious onset, with general malaise and often an initial pulmonary lesion. (2) No obvious focus of infection. (3) The fibrous process envelops, but does not invade, contiguous structures. (4) The renal tract above the prostate is always involved. This may occur at any level from the kidney to the bladder, but the brunt of the disease falls on the ureter(s), with secondary hydronephrosis causing severe renal damage. Mr. Power's case, whose successful outcome is a tribute to his skill, does not fulfil any of these criteria. The condition found in his patient is easily explained by the inevitable infection of cellular planes.

The profusion of names applied to idiopathic retroperitoneal fibrosis (periureteritis plastica, periureteritis obliterans, Gerota's fasciitis, sclerosing lipogranuloma, etc.) is sufficient indication of the existing confusion about the aetiology and pathology of this condition. I feel that the issue will be clouded still more if conclusions are drawn from cases which should not be included in this classification.

In my own contribution[2] to the subject I suggested a partially controlled infection as the underlying cause. Similar views have been expressed by Vest and Barelare,[3] Hutch,[4] and Mulvaney.[5] I have therefore been surprised not to have encountered a case, as yet, in an African patient. At least 85% of these, in this region, are infested by *Schistosoma haematobium* and almost all of these have superadded secondary infection. Also, the later stages of bilharziasis produce marked fibrosis of the ureters and bladder, and this combination should provide an ideal basis for retroperitoneal fibrosis if infection is a major factor. In an excellent review of possible causes, Hoffman and Trippel[6] present interesting evidence to support their view that the process is really a hypersensitivity reaction, possibly triggered by infection, and similar to periarteritis nodosa. This concept would be in keeping with Raper's[7] original suggestion.—I am, etc.,

Bulawayo, S. Rhodesia. WILLIAM HOUSTON.

REFERENCES

[1] Raper, F. P., in *Modern Trends in Urology*, 1960, 2nd series, edited by E. Riches. Butterworth, London.
[2] Houston, W., *Brit. J. Urol.*, 1957, **29**, 38.
[3] Vest, S. A., and Barelare, B., jun., *J. Urol. (Baltimore)*, 1953, **70**, 38.
[4] Hutch, J. A., Atkinson, R. C., and Loquvam, G. S., ibid., 1959, **81**, 76.
[5] Mulvaney, W. P., ibid., 1958, **79**, 410.
[6] Hoffman, W. W., and Trippel, O. H., ibid., 1961, **86**, 222.
[7] Raper, F. P., *Proc. roy. Soc. Med.*, 1955, **48**, 737.

Seasonal Incidence of Clinical Onset of Hodgkin's Disease

SIR,—I read with interest Dr. Marion D. Cridland's article (September 2, p. 621). It prompted me to review similar cases admitted to Guy's Hospital during the ten-year period 1950–9. The criteria for selection of cases were those of Dr. Cridland. During this time 98 cases of Hodgkin's disease were admitted. Of these, 48 were excluded from analysis because the time of onset was doubtful, and a further 20 cases because the disease was not localized. There remained 30 cases for analysis. The seasonal incidence of the clinical onset of these 30 cases, and of the 25 cases excluded because their disease was not localized, is shown in the table.

	30 Localized Cases with Definite Time of Onset		20 Cases Excluded because Disease not Localized	
	No.	%	No.	%
January	2	6·7	3	15
February	1	3·3	0	0
March	3	10	1	5
April	1	3·3	2	10
May	6	20	4	20
June	2	6·6	1	5
July	1	3·3	0	0
August	0	0	1	5
September	5	16·6	4	20
October	1	3·3	2	10
November	3	10	0	0
December	5	16·6	2	10

This study involves only a small number of cases, but it will be seen from these results that the incidence of clinical onset in May and September is high in both groups, but whether this indicates that there is a real seasonal incidence is debatable. The results certainly differ from those of Dr. Cridland.—I am, etc.,

Department of Medicine, Guy's Hospital Medical School, London S.E.1. R. D. HILL.

SIR,—I would like to congratulate Drs. James Innes and Joseph Newall (September 16, p. 765) for their promptness in analysing the seasonal incidence in their cases of Hodgkin's disease after the publication of my article (September 2, p. 621). It may interest them to know that in four instances in the London cases the time of onset of Hodgkin's disease was described as "early" in the particular year. These, of course, were not included in the series. It is possible that more specific information might have boosted the January incidence to 16%.

With regard to Dr. K. W. Beetham's implication of a festival incidence of Hodgkin's disease (September 30, p. 896), I must admit that I had also considered it and had, in fact, deleted a paragraph to this effect from the final article. In only one of the 23 cases was there specific mention of Christmas, five were recorded as "early in December" and three occurred in the last few days of the month. The remainder were recorded

as simply "December." If October proves to be the peak in Hull, we should expect news of a peak at Thanksgiving in America or one at the Jewish New Year in Israel.—I am, etc.,

Chester Beatty Research Institute, Institute of Cancer Research, London S.W.3. MARION D. CRIDLAND.

Isotope Studies of Portal Circulation

SIR,—The work of Drs. M. Salah Ibrahim and M. F. Abdel-Wahab (September 2, p. 623) has been received with great interest. At the University of Rochester School of Medicine and Dentistry we have continued our efforts directed toward isotopic evaluation of the portal circulation. Approximately 100 patients have been studied using the technique of percutaneous injection with an isotope into the spleen and simultaneous monitoring of radioactivity over the liver, heart, and oesophagus. Initially the technique was correlated with splenic-pulp manometry and splenoportography. Diagnostic patterns have been established for the normal portal circulation, patients with portal hypertension without varices, oesophagogastric varices, portal vein thrombosis, and portal-systemic shunts. Our initial investigations have been published in the *Journal of Nuclear Medicine* (1961, **2**, 85). The expanded work is to appear shortly in *Surgery*.

The apparatus is portable; thus the technique is particularly applicable to the emergency differential diagnosis of upper gastro-intestinal bleeding. Electively, it complements the splenoportogram in affording an evaluation of the dynamics of portal circulation and is particularly appropriate in the study of hepatic-portal encephalopathy.—I am, etc.,

University of Rochester School of Medicine and Dentistry, Rochester 20, New York, U.S.A. SEYMOUR I. SCHWARTZ.

Plantar Warts

SIR,—Dr. R. M. Clark's advocacy (September 30, p. 894) of radiotherapy for plantar warts is to be deplored. Even an alleged failure of other methods of treatment can be no justification for the employment of such a potentially hazardous form of therapy for a condition so exceedingly prevalent and so benign, though admittedly disabling.

Apart from the now widely recognized dangers of irradiation—and possible injury in children (by far the largest group of sufferers from plantar warts) to underlying epiphysial centres should not be forgotten—few dermatologists of experience have failed to become impressed by the notorious unpredictability of radiotherapy's capacity for cure even when employed in high dosage, and one has even seen a surviving and flourishing wart on a bed of radio-dermatitis.

The efficacy of any form of treatment in a condition so susceptible to suggestive influences is difficult to assess, and it is not rare for plantar warts to disappear spontaneously. Some investigators, moreover, have found that "*x* rays" work equally well when in fact they are not given, and the patient lies under the impressive apparatus in the mistaken belief that it has been switched on.

Though an absence of sequelae has been claimed by Dr. Clark, "long-term follow-up" may in fact not have been long enough, since it is known that such sequelae may not appear until an interval of very many years has elapsed. It is not surprising, therefore, that, as rightly pointed out by Dr. C. F. H. Vickers (September 16, p. 743), radiotherapy as a form of treatment for plantar warts has fallen into disrepute.—I am, etc.,

Wolverhampton, Staffs. H. W. CHADFIELD.

Lolly Rash?

SIR,—I have been following with great interest the correspondence on the above subject.

In reply to Dr. H. J. Kingsley's letter (September 30, p. 897), I would describe the rash in question as being mainly erythematous in nature, irregular in pattern, and confluent in parts. The distribution was mainly on the chest and abdomen, occasionally on the face and rarely on the limbs. It did not irritate very much, and cleared up completely in a few days. In all cases but one it was not raised, the exception being one case of a papular eruption.

It would seem that this rash differs in many important features from that described by Dr. Nevil Silverton (September 23, p. 831). Furthermore, I find it difficult to understand why Dr. Silverton describes erythematous macules as being one variant of papular urticaria, as by definition the former is not raised whilst the latter is. I should add that I am not a semantic, but appreciate the use of words which have a practical definition.—I am, etc.,

Plymouth, Devon. ALUN LLOYD-JAMES.

Aims of Criminology

SIR,—The holiday season interferes with one's reading, so I hope you will accept my apologies for bringing up at this late date your leading article on "Aims of Criminology" (August 12, p. 436). You remark that in criminology "methods of controlled experiment are not possible in this field." Ignoring the specific example you mention [flogging], since this is irrelevant, I would be grateful if you would inform me why controlled experiment is impossible, since it would appear that the problem of appropriate treatment for offenders is remarkably similar in its nature, from the point of view of research, to that of the treatment of patients.—I am, etc.,

Department of Psychiatry, Leeds University School of Medicine. MAX HAMILTON.

Health and the Commonwealth

SIR,—Now that the National Association for Prevention of Tuberculosis in the United Kingdom, having successfully dealt with the problem of tuberculosis, has changed its name to embrace the diseases of the chest, would it not be helpful if it took up the matter of the prevention of disease and disability as a whole and set itself up as a Commonwealth organization to create and guide similar bodies in the various countries of the Commonwealth? What I have in mind is a voluntary organization in every country whose task it would be to promote health in the widest sense. It would have to have representation from all sides of the nation's life if it was to perform its function properly.

We have at the moment in almost all countries of the Commonwealth a number of organizations against many types of disease and disability, such as associations for the prevention of malaria, venereal diseases, tuberculosis, leprosy, cancer, diabetes, trachoma, blindness, etc. Their numbers increase apace with the many specialties into which medicine is splitting. But

unfortunately, funds and trained personnel being not unlimited, there is waste in these directions from duplication and overlapping. All this could be avoided by the creation of a central organization, which could formulate policy, ascertain the extent of available amenities and resources, and make plans to meet the needs in the various fields by pooling the available resources. The results obtained by such unified and well-directed efforts would be worthy of the effort and money expended. The main function of the central organization would be to prepare plans in the light of advances in science and technology, and to give direction to a similar central organization in each country to pursue measures suited to meet local requirements in each project.

As the N.A.P.T. has the experienced and trained personnel and the administrative set-up, it seems to me that the N.A.P.T. is best suited for this purpose, not as a tuberculosis association as such, but as one that can readily set itself up as an organization suited to pursue the new objective by changing its name and aims. There is, of course, the World Health Organization, which is rendering excellent service all over the world. However, I feel convinced that the problem of health in the Commonwealth countries can be tackled expeditiously and efficiently and with greater co-operation as these countries have already existed as a unit for a considerable number of years.

This letter is based on a question on this topic which I posed over the B.B.C. Overseas Service and to which Professor C. Fraser Brockington, of Manchester University, replied in September, 1959.

—I am, etc.,

Colombo, Ceylon. A. Viswalingam.

"Pethilorfan" for Minor Orthopaedic Procedures

Sir,—As a result of reading Mr. J. R. Pearson's memorandum (March 5, 1960, p. 706) describing the use of "pethilorfan" (pethidine and levallorphan tartrate) in minor orthopaedic procedures, a trial with this drug was started in this unit in June, 1960. Although controls were not used, it was felt that the results of one year's experience with this method in a variety of conditions would be of interest to your readers.

The series comprised 38 patients, most of whom were young men who had sustained fractures in or near joints, followed by prolonged immobilization in plaster. Our main aim was to ensure relaxation in order to manipulate a stiff joint that had not responded to normal rehabilitation procedures or to physiotherapy. A small number of patients with chronic strains, particularly back strains or similar conditions, were also included.

The following technique was used. The patient lay on a physiotherapy plinth in a quiet room, and the pethilorfan was given intravenously in a dose of 150 mg. to 250 mg., depending on body weight. The injection was made slowly over at least two minutes and the respiration and pulse rates were checked for up to 30 minutes after the injection. The patient was told that he would not lose consciousness but that he would become sleepy and would feel little or no pain. About ten minutes after the injection the manipulation was carried out, as it usually took this time for an adequate state of drowsiness, euphoria, and relaxation to develop.

As regards the results, we found that muscle relaxation and inhibition of spasm during the manipulation was almost uniformly good, relaxation being sufficient in most patients to enable a satisfactory manipulation to be carried out. In fact, only one patient failed to relax adequately. On the whole, the analgesic effect was poor, as none of the patients would admit to the absence of pain during the actual manipulation. However, a rather unusual but none the less constant finding was that, after recovery from the effects of the drug, very few of the patients had any recollection of pain during the procedure. As a consequence, none of them raised any objections if it proved necessary to repeat the procedure at a later date. Most patients fell asleep after the injection and did not wake or recover fully from the effects of the drug for some two to three hours. Although this appeared to be normal sleep, patients were difficult to rouse and this seriously limited the value of the drug for out-patient procedures. One or two patients complained of headaches, mild nausea, or dizziness for up to twelve hours following the injection.

We concluded that "pethilorfan" is an interesting drug which produces useful muscle relaxation for minor orthopaedic procedures. It is not a very effective analgesic and its sedative effect is too prolonged for routine out-patient procedures. However, the drug could be valuable in those procedures in which a general anaesthetic is not justified or is not readily available. The amnesia produced in almost all patients is one of its most useful properties, in that patients will not object to serial manipulations if this should prove necessary. With the dosage used in the present trial, the drug does not appear to have any serious or alarming side-effects. —We are, etc.,

D. S. Smith.
J. B. M. Milne.
V. B. Whittaker.

Army Medical Rehabilitation Unit, Saighton Camp, Chester.

Prolonged Bleeding-time and A.H.G. Deficiency

Sir,—The case described by Dr. I. J. Carré and his co-workers under the above title (September 9, p. 682) presents most interesting and unusual features. May I be allowed to make the following comments?

The presence of Bridge anticoagulant would render inaccurate the estimation of antihaemophilic globulin.[1] Under such circumstances a precise estimation of antihaemophilic globulin (A.H.G.) is only possible when Bridge anticoagulant neutralizing agent[2 3] is used to counteract the inhibitory action of the plasma (unpublished work). It is possible, however, to obtain a reliable indication as to the possibility of spontaneous bleeding in a haemophilic or Christmas-disease patient by the simple method I described in these columns (May 6, p. 1321). This gives the balance between the activities of A.H.G. and Bridge anticoagulant.

The following observation might throw some light on the absence of haemarthrosis in spite of the presence of Bridge anticoagulant (concentration not mentioned, but presumably of a high level in this case). Of 196 cases of haemophilia and Christmas disease considered to be susceptible to spontaneous bleeding (as shown by the above method) four did not suffer from haemarthrosis although they were subject to spontaneous haemorrhagic episodes in other organs.[4] The patient reported by Dr. Carré and his colleagues, having spontaneous gastro-intestinal haemorrhages, would appear to be similar to this small group.—I am, etc.,

F. Nour-Eldin.

Southmead Hospital, Bristol.

References

1 Nour-Eldin, F., and Wilkinson, J. F., *Brit. J. Haemat.*, 1958, **4**, 292.
2 —— in *Proceedings of the 7th European Congress of Haematology, London, 1959*, vol. 2, p. 599.
3 —— *Nature (Lond.)*, 1959, **184**, 1419.
4 —— *Lancet*, 1961, **1**, 1233.

Spontaneous Delivery of Central Placenta Praevia

SIR,—I have been interested to read accounts of this event from Newfoundland (Dr. John Weeks, June 3, p. 1589), from Uganda (Dr. P. S. Sanade, August 5, p. 384), and from India (Dr. Betty Holt, September 16, p. 766). With the influx of immigrants of African and Asian origin into the United Kingdom we can now expect such events to be repeated over here. I have to report a similar occurrence as recently as November 16, 1960, where the patient was a Sikh woman expecting her third baby.

This patient had already had two normal confinements in the district of Jullunder, Punjab. Her husband brought the family over to Slough early in 1960, and her third baby was expected about February 4, 1961. She was booked at a maternity home under the N.H.S. on grounds of overcrowding at home, and her blood-group was obtained by the maternity home.

On November 16, 1960, when she was at her thirtieth week, she came into labour. I was called to her home at 11 p.m. and found her with a moderate show, staining only one diaper and not the sheets, and with pains occurring every three to five minutes. Vaginal examination disclosed ruptured membranes and cervix three-quarters dilated, with a foot and approximately half the placenta extruding through the os. As the loss was not severe I was posed with the dilemma: Was it going to become severe and should I send for the "flying squad," or should I rather move her immediately to the hospital, which was half a mile away, as her condition so far as blood loss was concerned was good?

I plumped for the latter and called the ambulance first before asking the nearest hospital for a speedy admission. I accompanied the patient to hospital, rang the maternity home for the blood group, and the blood was obtained. But it was not required. The placenta was shot out ahead of the breach, exactly half an hour after our arrival in hospital, and all was well except for the fact that the loss of a male baby was greatly deplored by the Sikh family.

I agree with Dr. Sanade that, if the cervix is dilating well and there are good and frequent contractions, the placental site in the lower segment of the uterus will not bleed excessively, as the placenta is squeezed away from it. The foetal head was not applied to the placenta in my patient, but the knees "kneaded" it during expulsion.—I am, etc.,

Slough. N. C. HYPHER.

Sobering-up

SIR,—I was interested to read Dr. Bruce H. Boeree's letter (August 19, p. 524) regarding rapid "sobering-up" by giving nikethamide intravenously.

This method was used by me as a house-officer in 1953, when on duty as casualty house-officer, with nearly disastrous results to myself. A man was brought in comatose after drinking gin for half a day. It was about 9 p.m. when he was brought in, and his wife, who accompanied him to the ward, was convinced that he was dead and wanted me to assure her that the man was still alive. I gave him 4 ml. nikethamide intravenously, not too fast. Before I had finished the injection the patient showed signs of life. By the time I had withdrawn the needle he had begun to make violent movements. He sat up in bed, looked around him, and then jumped at me to strike me. I dodged out of the way and let the male attendants hold him down. He turned abusive and demanded to know why he was in a strange place. He refused to believe that he was in hospital and insisted on going home. The wife signed the bed-head ticket and took the man home. She returned the next day to say that her husband had assaulted her when they got back home, and had then gone to sleep and slept right through till morning.

It would be advisable when giving large doses of nikethamide to this type of case to have assistance at hand to control a boisterous patient.—I am, etc.,

Nuwera Eliya, Ceylon. DENIS H. M. VARNEY.

Neuropathy after Thalidomide

SIR,—Drs. Pamela M. Fullerton and Michael Kremer (September 30, p. 855) state no similar toxic effects have been observed in patients taking "doriden" (glutethimide). I wonder none the less if less severe, but attributable, effects occur.

I have taken a half-tablet of doriden each night (half the suggested minimum dose) for three years to get to sleep after waking in the early hours. In this period I have had several attacks of severe cramp in the calves or in my feet, lasting several days each time and really bad (on one occasion I leapt up in a dentist's chair, and he thought he had hurt me, but it was another attack of cramp in my foot). I had to take more doriden during these episodes as sleep was almost impossible. My palms have been red. Also, I have had several attacks of gross muscle twitching, involving different areas at different times—naso-labial, palpebral, and vastus externus, and persisting two or three days on each occasion. My legs feel weak and I tend to slip readily on inclines and several toe-nails are now split. I have not tested for sensory changes.

I feel impelled to record these personal symptoms, though they may well have nothing to do with my nightly small dose of doriden, in case anyone else on this drug has had similar experiences. I take practically no alcohol.—I am, etc.,

Horam, Sussex. L. C. F. CHEVENS.

Lignocaine with Adrenaline

SIR,—May I endorse the remarks of Drs. D. D. Craig and C. J. Levy (September 23, p. 826) with regard to the dangers of lignocaine 2%? A recent paper[1] has condemned the practice of using the drug in this strength. Lignocaine should be used in a concentration of more than 1% only for special purposes such as spinal or epidural analgesia, for topical application, or in dentistry. The dose for an adult should not exceed 500 mg., and if the patient is a child a proportionally smaller dose limit should be applied, calculated on the basis of body weight. One of the manufacturers (Duncan, Flockhart and Co. Ltd.) has produced an excellent booklet dealing with the clinical use of the drug. A simple dosage card is also available.

Convulsions following overdosage are best controlled by means of thiopentone, and if this is not fully effective, or if respiration is inadequate, the use of suxamethonium and the administration of endotracheal oxygen are indicated.

Drs. Craig and Levy refer to "the fortunately only occasional fatalities due to the use of lignocaine." I have collected details of nine deaths, occurring in this country, associated with the use of lignocaine. Three recent cases may be described. Each involved the use of lignocaine 2% and each was the subject of an inquest. (1) A fit adult developed convulsions and respiratory

arrest after receiving 30 ml. of lignocaine 2%. (2) A boy of 4 died after 15 ml. of lignocaine 2% had been used to block the brachial plexus. (3) A boy of 9 died after being given 30 ml. of lignocaine 2% prior to the reduction of fractures. I have been unable to discover any instance of death due to sensitivity to lignocaine. Overdosage was responsible in all cases. Fatalities have probably occurred in addition to the nine mentioned above, and others must be expected if the indiscriminate use of lignocaine 2% continues.—I am, etc.,

Department of Anaesthetics,
The Royal Free Hospital,
London W.C.1. A. R. Deacock.

References

[1] Deacock, A. R. de C., *Anaesthesia*, 1961, **16**, 363.

Aspirin Anonymous

Sir,—I would like to write in wholehearted support of your correspondent who points out another of the dangers of pharmacological anonymity (September 30, p. 896). I had a similar experience of greater personal significance with the same preparation.

My father had a lifelong knowledge of the fact that aspirin makes him extremely ill. Whilst suffering from a minor stomach upset, combined with aphthous ulcers of the mouth, he took "alka-seltzer" on the advice of a friend and within hours had the most alarming haematemesis. For several days while being continually transfused he was gravely ill, the haemorrhage terminating with a partial gastrectomy. Fortunately he survived this operation, the stomach showing multiple shallow erosions, but has remained to some extent an alimentary invalid ever since.

I believe that all drugs should be clearly labelled, preferably without even the concealment of a trade name. Certainly the statutory labelling of drugs liable to cause death from hypersensitivity or allergy should be a minimal requirement.—I am, etc.,

Queen Elizabeth Hospital,
Birmingham 15. B. N. Williams.

Sir,—Dr. D. B. Davies (September 30, p. 896) has directed attention to the presence of aspirin in "alka-seltzer" and to a case of severe status asthmaticus resulting from the patient's allergy to aspirin and to her not knowing that alka-seltzer contained it.

It is three years since I suggested in your columns[1] that aspirin-sellers should be compelled to warn their customers of another hazard in its use, that of gastro-intestinal haemorrhage. In a second letter[2] I pointed out that alka-seltzer contained aspirin and was at that time being advertised to the public for the relief of indigestion. In a recent leading article[3] it was stated that "consumption of aspirin is an important cause of gastroduodenal bleeding and makes an appreciable contribution to the number of hospital admissions on account of haematemesis and melaena. Patients with peptic ulcers should be counselled against taking aspirin for the relief of incidental discomforts. . . ."

The present position is that alka-seltzer is still being extensively advertised to the public on commercial television and in the press for the relief of indigestion. This makes it quite certain that virtually all ulcer patients are being encouraged to take aspirin.

Aspirin is one of the most useful drugs in the book: and alka-seltzer is a splendid form in which to take it on certain occasions, as most of your readers will be able to testify. But it is indefensible that it should be advertised as at present, and I should therefore like to make a strong plea (*a*) that all preparations containing salicylates should say so in terms the lay customer will understand, and (*b*) that all containers of aspirin or preparations containing it should carry a clear warning for the ulcer-patient.—I am, etc.,

Department of Physiology,
The London Hospital Medical College,
London E.1. J. Dobbing.

References

[1] Dobbing, J., *Brit. med. J.*, 1958, **2**, 1226.
[2] —— ibid., 1959, **1**, 787.
[3] *Lancet*, 1961, **2**, 470.

A Drug Advertisement

Sir,—One is always glad to see references to reputable medical journals in trade literature. A recent circular began by referring to your article on non-virilizing androgens in the series "To-day's Drugs" (April 29, p. 1245), and continued: "Androstanolone ('anabolex') is placed high among the androgens listed." There followed mention of alleged diuretic and non-virilizing effects, and one turned to the article for verification. In fact the article quoted makes no specific mention of the pharmacological effects of this preparation, favourable or otherwise, it being merely listed with seven others with regard to name, dosage, price, and chemical composition. Its "high place" at the head of the list is solely due to the fact that the list is alphabetical.—I am, etc.,

St. Mary's Hospital,
York. E. Gordon Wilkins.

Nuclear War

Sir,—There are many eminent medical men in this and other countries who have the well-being of their fellow men at heart. Their opinions as scientists and as humanitarians would be valued and heeded attentively by peoples of different nations. So much so that I feel pressure would be brought to bear on governments which are careless and regardless of their peoples' welfare.

Surely the British Medical Association can lend a hand and perhaps even lead in this movement by soliciting the help of our most competent medical scientists, along with representatives of the general practitioners since they are in contact with public opinion, to meet with similar bodies throughout the world. In this way we can be sure that the dangers facing us all will be made known universally, and the swelling wave of public opinion should put a curb on irresponsible political gangsterism and make all governments take note. This should be able to be done without forming committees to form committees *ad infinitum*.—I am, etc.,

Liverpool 18. P. Marioni.

Insertion of Intravenous Cannula

Sir,—The problem of inserting a good-sized polyethylene tube into a vein without "cut-down" was raised by Dr. C. K. Jones (August 12, p. 456). The method he describes of using a polyethylene tube over a spinal needle was utilized in a needle devised and produced in the Mayo Clinic. The only difference was in the length of the needle, which in the latter was of usual length (1½–2 in.—3.7–5 cm.). This resulted in a short polyethylene tube being left in the vein. However, this method does not solve the problem, because to

introduce such a needle is possible only when the veins are large and prominent, and even so the polyethylene tube is not large enough for fast infusion of blood.

I have devised and used two instruments which allow the insertion of really large polyethylene tubing, even in small veins. The first one[1] required double puncture of the vein. I therefore devised another instrument which allowed the introduction of polyethylene tubing intravenously with one puncture.[2] The principle of this instrument was a guiding needle which was followed by a gutter accommodating the polyethylene tubing. The gutter with polyethylene tubing has to follow the path of a small-gauge guiding needle. In practice a large gutter with a large polyethylene tube can be quickly introduced without any difficulty in a small vein. This allows the use of polyethylene tubing more frequently in order to avoid many venepunctures during operation and in post-operative treatment, and is especially recommended in all cases where emergency replacement of blood during operation may be anticipated and where prolonged intravenous feeding in the post-operative period is necessary.—I am, etc.,

Sydney, Nova Scotia. C. Uhma.

References

[1] McDonald, F. B., *Canad. med. Ass. J.*, 1956, **75**, 760.
[2] Uhma, C. A. F., ibid., 1958, **79**, 1004.
[3] —— *Amer. Practit.*, 1959, **10**, 665.

Osteopathic Medical Association

Sir,—The Osteopathic Medical Association has been founded with the following objects: (i) To contribute towards the promotion and propagation of the science and art of osteopathy and hold professional and social meetings in furtherance of this aim. (ii) To demonstrate to registered medical practitioners the value of the science, art, and practice of osteopathy. (iii) To encourage research and the publication of results. (iv) To co-operate with other medical associations.

Membership is open to duly qualified medical practitioners registered in Great Britain who are interested in osteopathy. All inquiries will be welcomed.—We are, etc.,

Bledisloe, President.
Alan Stoddard, Vice-president.
John H. Davidson, Chairman.
M. E. B. Carson, Secretary.

114 Wigmore Street, London W.1.

A Case for Diagnosis

Sir,—It is just possible that a clue to the missing diagnosis of the case described by Drs. Zaida M. Hall and R. R. Wilson (September 23, p. 820) may be found on the cover of the *British Medical Journal* which depicts a serpent nestling in the arms of a suitably inscribed horseshoe. Calcified deposits of horseshoe shape (*fer-à-cheval*) may be the radiographic signature of an infestation of the tissues by *Porocephalus*, a primitive arthropod that lives parasitically in certain snakes. Multiple calcifications of this type are not infrequently discovered accidentally in the mesentery and lungs of Africans who eat snakes. This is an unusual patient with an unusual history. The question thus arises: did he, too, eat snakes?—I am, etc.,

Basle, Switzerland. Michel Fernex.

*** We showed this letter to Drs. Hall and Wilson, who reply as follows: "We had already considered the possibility suggested by Dr. Fernex but had discarded it for three reasons. First, the patient was very emphatic that he had never eaten a snake. Second, it seems improbable that a presumed infestation acquired in 1942–3 should cause lung lesions which evolved and sclerosed during the period 1949–61. Thirdly, none of the many sections from the three biopsies yielded any indication of parasitic infestation." —Ed., *B.M.J.*

Medical Aid to Developing Countries

Sir,—Of 7,789 medical practitioners registered in the Union of South Africa in 1959 only 67 were African and 93 Indian and coloured (approximately 25% of the total population is white). By closing all medical schools but one (Durban) to non-white medical students at the beginning of 1960 the policies of apartheid are enabling only a fraction of non-white would-be medical students to embark upon their course of studies.

Since this committee came into being some 14 months ago we have been inundated with requests for help, and we have now written to the deans of all medical schools in the U.K. asking them to consider making available scholarships for some of these medical students in this country. The issue is to be fully discussed at an open meeting to be held at B.M.A. House on Thursday, October 26, at 8 p.m. We hope that those who have the matter at heart might join us on that evening.—I am, etc.,

Eleanor Ettlinger, Secretary, Medical Committee Against Racial Discrimination in South Africa.

London W.11.

POINTS FROM LETTERS

Filter-tip Cigarettes

Dr. Dick Glover (Guildford) writes: Filter-tip cigarettes are becoming more and more popular. As a smoker I find that the last half-inch or so of a filter-tip cigarette tends to make me cough. Could this be due to the fact that the smoke has to pass through a build-up of trapped tar in the filter? If this is the case surely an even distribution of irritant substances throughout the cigarette would be less harmful than a concentration of them in the filter? In other words, non-filter-tip cigarettes should be less harmful.

Enzymes and Disseminated Sclerosis

Dr. J. A. Frais (Shipley, Yorks) writes: With the recent discoveries of the chemical relationship between depression and monoamine oxidase and blood serotonin levels, one is prompted to ask if any research has been directed towards the possibility that the very marked euphoria in disseminated sclerosis may in fact be due to a chemical upset caused by overaction of one of the newly discovered enzymes which act on personality. It might then be postulated that such actions could in turn cause organic lesions in the cord with the only too well-known results.

What the Doctor Said

Mr. H. Robinson, L.D.S. (Worthing), writes: Dr. F. R. C. Casson's letter (September 30, p. 900) recalls to my mind a girl in the north who told me her father had been to see an eye specialist who told him he was suffering from "miner's stagnation."

Pyrimethamine and Polycythaemia Rubra Vera

We much regret an error that appeared in Dr. J. L. Stafford's letter (October 7, p. 960). The drug name tretamine was wrongly substituted for busulphan in his last paragraph. The relevant part of his letter should have read: "At this point an effective oral therapeutic agent is a great assistance. In such instances busulphan is probably preferable, for it is more effective in its depression of the white cell mass which is usually raised at this stage, and in the long run patients tolerate it much more readily."—Ed., *B.M.J.*

Obituary

NEWTON HEATH, F.R.C.S.Ed.

Mr. Newton Heath, orthopaedic surgeon to the Royal Hospital, Wolverhampton, and the Guest Hospital, Dudley, died on September 26, aged 62.

Newton Heath was born at Chippenham on February 9, 1899. Even as a schoolboy he had shown an inclination towards a life devoted to religious work. He was old enough to join the Army towards the end of the first world war, but saw no active service. Seconded as a student cadet to Balliol College, Oxford, when the war ended he entered Keble with the intention of taking Holy Orders. During his time there he became more and more interested in the work of medical missionaries. Having taken an arts degree he proceeded to M.A. in 1925. By then he had decided to qualify in medicine, and in order to finance his studies he spent some time as a master at Clifton College. He then obtained an entrance scholarship to Westminster Hospital, where he qualified in 1931. He held various resident appointments there, finally becoming general surgical and orthopaedic registrar. Here he came under the influence of Sir Ernest Rock Carling, with whom he found much in common. He obtained the F.R.C.S.Ed. in 1937 while working as resident surgical officer at Walsall General Hospital. The excellence of his character and work was noted by several members of the staff of that hospital who were also on the staff of the Royal Hospital, Wolverhampton. When, therefore, in 1939 it was proposed to increase the orthopaedic staff at Wolverhampton he was readily elected in July, 1939, to the post of registrar, with an expectation of his being promoted to the consultant staff.

With the outbreak of war Heath, who was a member of the R.A.M.C.(T.) reserve, left the hospital for war service, most of which was spent abroad. He gave outstanding service in the Army, first in France, Northern Ireland, and Nigeria. Seconded to the Royal West African Frontier Force, he was officer commanding the General Hospital in Nigeria. He served in India and South-east Asia for nearly three years and later in the African campaigns in 1944 and 1945. At one time he was in command of a 1,200-bed hospital. He was awarded the Territorial Decoration in 1950.

On his return to civilian life in 1946 he was at once elected to the staff of the Royal Hospital and to the Guest Hospital, Dudley. Heath lived a life of almost monastic simplicity, and devotion to his work left him little time for social life. He had an excellent physique and played games well—especially was he an outstanding member of the staff cricket team. His main recreation was walking in the remoter parts of Wales and Scotland. In his earlier days he had been much interested in music, especially church music, and had been a good violinist.

A reticent man, he was not one whose reserve could quickly be pierced, but the more we knew of him the greater was our estimation of him as a man. As a colleague he was universally liked. His gentleness and kindness to his patients was a by-word. When the inevitably fatal nature of his illness was apparent he accepted the situation with the calm courage that we should have expected of him.

He was not married. His passing is mourned by all his colleagues.—E. A. F.

E. J. C. BOCKETT, M.B., B.S.

Dr. E. J. C. Bockett, who practised in Farnborough, Hampshire, died at Cork, Ireland, on September 25. He was 62 years of age.

Eric John Cuming Bockett qualified from King's College Hospital in 1926, graduating M.B., B.S. three years later. After holding several house appointments at his teaching hospital and at the Belgrave Hospital for Children and the Hampstead General Hospital, he went into a partnership in Farnborough. There he soon became one of the leading medical men in the district, holding the appointment of surgeon at Farnborough Hospital and at the Frimley and Camberley Hospital. In addition he was deputy coroner for the Aldershot district.

F. B. writes: Eric Bockett died, as I think he would have wished to do, in harness. It is eminently true in his case that he wore himself out in the service of others, and he refused to spare himself despite a severe cardiac illness three years ago. His end, although sudden, was not altogether unexpected.

He was a man of remarkable qualities, of which patience, single-minded devotion, and a painstaking thoroughness were the chief. He served for a period of 30 years on the staff of the general-practitioner hospitals at Farnborough and Frimley—since 1948 in a surgical and consultant capacity—and his colleagues have many happy recollections of his wise and valued help. He had trained himself to be a first-class obstetrician. I remember in our student days Sir William Gilliatt being asked, "What do you do in the heat of the moment?" and his reply, "There is no such thing as the heat of the moment in obstetrics." This well illustrated Eric Bockett's approach to both his obstetrics and his surgery. I think he was happiest when operating at the Frimley Hospitals—a classical caesarean section, a "tonsil" session on a Saturday afternoon, a difficult appendix late at night, when the combination of painstaking surgery and an indifferent anaesthetist left him calm and unruffled. He was a first-class committee man—chairman of the local division of the B.M.A. in 1955–6 and a member of the medical advisory committee of the Farnham Group since its inception in 1948.

Generous to a fault in his personal relationships, he was a devoted family man, and his daughters and his grandchildren gave him great pride and joy. Our sympathy goes out to his wife, herself a member of the profession; his daughter Mary, a physiotherapist trained, like her father, at King's College Hospital; and his daughter Joan, the mother of his two grandchildren.

J. W. McK. NICHOLL, M.D.

Dr. J. W. McK. Nicholl, who practised in Lewes, died at sea on September 19, aged 66. He was returning from a visit to his younger daughter in Australia.

Joseph Warren McKillop Nicholl was born at Amritsar in Northern India on October 11, 1894, and educated at Christ's Hospital, Queens' College, Cambridge, and the Middlesex Hospital. At Cambridge he was president of the Cambridge Intercollegiate Christian Union in 1915, and took an active part in the spiritual life of the university. A keen Rugby footballer, he played for the Old Blues, Kent County, and the United Services, and in later life he was president of the Sussex Rugby Union and a founder member of the Lewes Rugby Club. After qualifying in 1917 he became a house-surgeon at the Royal Sussex Hospital at Brighton, from there joining the Royal Navy as a surgeon lieutenant.

After the first world war he married Gladys May Chancellor, and subsequently went with his wife and young family to Quetta in North India as a medical missionary with the Church Missionary Society. Previous to this he had graduated M.B., B.Ch. at Cambridge. He worked with Sir Henry Holland in the mission hospital and gained much valuable experience in general surgery and eye work. Later on he often spoke of that time as being some of the best years in his life. In 1922 he obtained his M.D. with a thesis on subacute bacterial endocarditis.

He returned to England in 1925 and settled as a general practitioner in Lewes, Sussex, where he remained for 36 years, becoming a distinguished surgeon on the staff of the Victoria Hospital, Lewes. Affectionately known as "Joe,"

he was held in great esteem by nurses and patients alike. Among his many appointments were those of surgeon to the East Sussex Police, local Treasury medical officer, and M.O. to Lewes Prison. His services to the St. John Ambulance Brigade were recognized by his appointment as Officer (Brother) in the Venerable Order of St. John of Jerusalem. For 33 years he was leader of the Crusaders Bible Class in Lewes. He lived to see his youngest son mayor of Lewes for the year 1959.

A man of varied and all-round interests, he made a great many friends, and his home was open to all: with his large figure and beaming smile, he greeted everyone on his doorstep. He was at heart a deeply religious man with a wide sympathy both professionally and socially, and if there was a particular trait in his character which was outstanding it lay in his power to produce a calm atmosphere in an emergency, whether in the operating theatre or elsewhere—perhaps the result of his early training in the Navy.

He leaves a widow, three sons, two daughters, and 16 grandchildren. The sympathy of all his colleagues and friends will go out to his widow and family for their great loss and ours.—H. D. C. R.

LAWRENCE REYNOLDS, M.D.

Dr. Lawrence Reynolds, one of the leading radiologists in the United States, died suddenly on August 17 at the age of 72. For many years chief of staff of the Harper Hospital, Detroit, he had also been clinical professor of radiology at Wayne State University College of Medicine.

Lawrence Reynolds graduated in medicine from Johns Hopkins Medical School in 1916 and later served with the American Forces in France during the first world war. Having been instructor in roentgenology at the Johns Hopkins and Harvard Medical Schools, he began radiological practice in Detroit in 1922. His association with the Harper Hospital there was always a close one. He soon rose to an eminent position in his specialty and from 1930 until his death he was editor of the famous journal now known as the *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine*. An ardent bibliophile, his advice was sought by many libraries and learned societies.

Dr. Russell Reynolds writes: Dr. Lawrence Reynolds had been a personal friend of mine for many years, and we corresponded with one another frequently during this period. Whenever I visited the U.S.A. either lecturing on radiological subjects or attending radiological congresses as the British representative we always managed to meet. Lawrence was certainly one of the pioneers of radiology in the U.S.A. He was past-president of the American Roentgen Ray Society and the American College of Radiology, and he received the highest awards of a gold medal from the Radiological Society of North America and also from the American College of Radiology. He was an honorary member of many radiological societies in Europe and the United States. In him the Harper Hospital has certainly lost a great friend and physician.

FRANK GUIVER, M.R.C.S., L.R.C.P.

The death of Dr. Frank Guiver occurred at the Essex County Hospital, Colchester, on August 19 after a short illness.

Frank Guiver was born on August 26, 1898, at Enfield, and was educated at the City of London School and the London Hospital, where he qualified in 1923. In 1924 he joined Dr. Sidney Brée at Manningtree, Essex, as assistant. On becoming a partner he moved to Ardleigh, where he continued to practise until his death.

A G.P. of the old school, he never spared himself when he could be of service to his patients, spending many hours of every day devoting himself to their care and personal problems. His patients rewarded him by their complete devotion and loyalty, and hundreds are now surely mourning his loss. He had built an extensive practice in conjunction with four partners who will miss his dominant and cheerful personality which directed partnership affairs with such great ability. Frank Guiver's busy life left little time for hobbies or recreation, but he enjoyed a game of bridge and loved his garden. His holidays abroad, to which he always looked forward, gave him scope to exercise his skill as a photographer.

He married Miss V. Brée, daughter of his first partner, in 1925, and he always paid tribute to the great help and comfort she gave him during his very busy life. He is survived by his wife, two sons, and one daughter, the elder son being a partner in his old practice.—J. G. S.

C. Y. ROBERTS, M.R.C.S., L.R.C.P.

Dr. C. Y. Roberts died on September 10 in Sheffield, where he had practised for nearly 30 years. He was 70 years of age.

Charles Young Roberts was born in Torquay on March 21, 1891. He studied medicine at St. Thomas's Hospital, qualifying in 1916. After serving in the R.A.M.C. until 1919 he became a partner in a practice in Scarborough. In 1922 he enrolled as a medical officer in the R.A.F. and served in India until 1925, when he joined the Cunard Company as a ship surgeon, serving in the *Mauretania, Lancastria,* and *Corynthia*. In 1932 he took over a practice in Glossop Road, Sheffield, where he stayed until his retirement in September, 1960.

H. M. H. writes: Charles Roberts was a fine gentleman who never said an ill word about anybody. He was genuinely loved by his patients, for whom he took infinite trouble. Human nature being what it is, his kindness was not infrequently taken advantage of and he spent many nights visiting patients whose consideration for him did not match his high standards of service. He had little time for academic medicine, having gained his knowledge in the hard school of panel practice, and he had many a tip to pass on to a younger man. He was a very happy and hospitable man whose views were in full agreement with those recently expressed by the Archbishop of Wales. No visitor left his house unless amply refreshed and with a rosier outlook on life. He will be sadly missed by his friends, his widow, and his family, to whom we extend our deep sympathy.

ELZBIETA E. GIELNIEWSKA, M.R.C.S., L.R.C.P.

The untimely death of Dr. Elzbieta Gielniewska at the age of 37 took place on September 30. She was a psychiatric registrar at Severalls Hospital, Colchester, Essex.

Elzbieta Ewa Gielniewska was born in Warsaw, her mother being English. Having survived the war in Poland, she qualified in medicine in 1952 and subsequently worked as a medical officer in the British Embassy in Warsaw. She came to England in 1954 and made her home here. Having held an appointment as house-physician at Black Notley Hospital, she succeeded in passing the examinations for the Conjoint diplomas in 1958.

Her work at Severalls was characterized by kindness and sympathy, which she extended to all her patients. It was rare that she was unable to coax a response from even the most chronic psychotic long-stay patients. Her knowledge of general medicine was both wide and thorough, and she was a most conscientious and painstaking doctor. The interest in psychiatry which she pursued successfully resulted in an increasing competence in dealing with patients with psychiatric disorders.

She was beloved by those who got to know her, and her sudden and unexpected death from a massive subarachnoid haemorrhage came as a severe shock. She will be sadly

missed by her circle of friends, colleagues, and patients. Our sympathies and condolences go out to her sister, Mrs. Bendnarcyk, now residing in Vienna.—R. B.

H. M. ROYDS JONES, M.D.

Dr. H. M. Royds Jones, who was until recently a medical officer on the staff of the Shipping Federation Ltd., died some weeks ago in the Royal Free Hospital. He was 64.

Herbert Martin Royds Jones came of a family of doctors and clergymen. After serving throughout the first world war, he studied medicine at the Middlesex Hospital, qualifying in 1924 and graduating M.B., B.S. in the following year. After holding house appointments at his teaching hospital and at the Brompton Hospital, he became a ship surgeon for many years, mainly with the Orient Line. He joined the Shipping Federation for a few years before retirement. He did some valuable work in connexion with the health of seamen while a ship surgeon and successfully presented his findings for an M.D. thesis in 1935.

G. O. M. writes: "R.J." represented the older school of practitioners who regarded medicine as a vocation and a prerogative of an English gentleman. His own dapper appearance and quiet firm manner expressed just this. When he gave an opinion it was stated succinctly with a business-like definiteness and simplicity which is so valuable to an employer in industry. He was splendid to work with—genial, quick but conscientious, and strictly ethical—and he had an engagingly subtle humorous insight into his own amusing bachelor's foibles which rather endeared him to his younger colleagues. It is a measure of the esteem in which he was held that associates twenty years his junior so much miss being able to write to him or visit him in his retirement. The profession cannot afford to lose practitioners like Royds Jones, who set an example of dignity that is a memento of better times than the present.

J. W. CRAVEN, *M.C.*, M.D.

Dr. J. W. Craven, formerly medical superintendent of the Auckland Hospital, New Zealand, died at Rotorua on July 19. He was 72 years of age.

Joseph Wilfrid Craven was born at Gosforth, Northumberland, on November 22, 1888. Educated at Bede School, Durham, and at the University of Durham, he graduated M.B., B.S. in 1912. After holding house appointments at the Royal Victoria Infirmary, Newcastle upon Tyne, he worked for a time as a ship surgeon for the P. & O. Steam Navigation Company. He had a distinguished career in the first world war, being promoted to lieutenant-colonel in the R.A.M.C., winning the Military Cross, and being appointed a Chevalier of the Legion of Honour. He was also mentioned in dispatches. He served throughout with the 1st Northumberland Field Ambulance and later commanded it. Continuing to serve after the war as a Territorial, he received the Territorial Decoration. After demobilization he worked for a time with the Ministry of Pensions in Newcastle and then in general practice.

In 1925 he went out to New Zealand and commenced practice in Birkenhead, a suburb of Auckland. Seven years later he was appointed medical superintendent of the Auckland Hospital and did splendid work in that capacity. His organizing ability and his kind, friendly disposition won him the respect and friendship of the honorary staff and of all who worked in the hospital. At the beginning of the second world war he was appointed to the command of the Queen Alexandra Hospital in Singapore with the rank of lieutenant-colonel, and on the fall of Singapore in February, 1942, he was taken prisoner by the Japanese and for a time was in command of the Changi prisoner-of-war hospital. He had a bad time and his health suffered severely. He was returned to New Zealand in 1945 and resumed his duties as medical superintendent of the Auckland Hospital. He had to resign, however, in 1949 owing to ill-health and retired to Rotorua. His resignation was received with great regret.

Dr. Craven was an excellent doctor and a most lovable man. He had a bright, cheerful disposition and radiated happiness all round. In his long last illness he exhibited great courage and fortitude and never complained. We extend our deep sympathy to his wife, who looked after him so faithfully and well, and to his son and daughter.—J. H. B.

R. Y. STONES, O.B.E., *M.C.*, M.D., M.R.C.P. F.R.C.S.Ed., D.P.H., D.M.R.E.

The obituary of Dr. R. Y. Stones was published in the *Journal* of October 7 (p. 966).

Sir PHILIP MANSON-BAHR writes: May I pay a tribute to my old friend Robert Stones? I have known him for more years than I like to think of, since we were together as students at the London Hospital and subsequently "on the house." I have always thought of Stones as a great practising Christian who was so clean and straightforward in his dealings with the sick and also with his fellow men that he gained universal admiration. When anyone was in trouble, be he what he might, Stones was there to help. He was no narrow-minded evangelist, far from it, he was a great human being ever there to grasp the proffered hand. He was a good sportsman and a game, courageous boxer who gave as good as he got, being by no means a poor performer. He was always ready to do his best whatever behove and, above all, he was a staunch and faithful friend. We corresponded regularly at Christmas-time for many years, especially when he moved on to Uganda after the second world war. Stones was indeed a great Christian gentleman whose one aim was to do good to others, and as such I shall always remember him.

Universities and Colleges

UNIVERSITY OF GLASGOW

The following appointments are announced: Dr. H. I. A. Nisbet, Lecturer in Anaesthetics; Dr. G. P. Lewis, Lecturer in Materia Medica; and Mr. R. J. McWilliam and Mr. R. J. S. Smith, Honorary Clinical Lecturer in Ophthalmology at Glasgow Eye Infirmary.

UNIVERSITY OF DURHAM

In Congregation on September 23, the degree of M.D. was conferred upon L. B. Strang (*in absentia*) and A. S. Todd.

UNIVERSITY OF BIRMINGHAM

The following appointments are anounced: Mr. J. C. Gray, Lecturer in the Department of Surgery, from August 1, 1961; Dr. G. Bentley, temporary lecturer in the Department of Anatomy, Dr. G. R. Kelman, Research Fellow in the Department of Medicine, and Dr. W. A. Marshall, Research Fellow in the Department of Anatomy, all from October 1, 1961.

UNIVERSITY OF LEEDS

The degree of M.D. was awarded to J. C. Woodrow in September.

Vital Statistics

Admissions to Scottish Mental Hospitals

During 1960 the number of certified patients in ordinary mental hospitals in Scotland fell by nearly 1,000 to 12,958, while the number of voluntary patients increased by 575 to 6,960, the total of 19,918 representing a net decrease of 358 compared with the 1959 figures. This was the fourth successive year in which there has been a reduction in the mental-hospital population of Scotland. Nevertheless the number of admissions continues to increase—from 5,764 in 1948 to 12,760 in 1960. The large increase in the number of voluntary admissions during the past years has been

accompanied by only a comparatively small reduction in the number of certified patients—2,608 in 1948 and 2,298 in 1960. Of the total number of admissions to mental hospitals during the year, 5,112 (40%) were of patients who had been in a mental hospital before (11% of the total number of patients admitted returning within three months of the last discharge).

In 1850 the admission rate to Scottish mental hospitals was 0.49 per 1,000 of the population, in 1900 it was 0.82, in 1950 it was 1.3, and in 1960 it had risen to 2.6.—*Annual Report of the General Board of Control for Scotland for the Year 1960*, H.M.S.O., Edinburgh.

Causes of Death in 1960

According to provisional figures issued by the Registrar-General deaths from *coronary heart disease* in England and Wales in 1960 totalled 91,961 (56,514 male and 35,447 female), an increase of 7,039 over the 1959 figure. In men, the greatest number of deaths (20,673) occurred in the age-group 45 to 64; in women, the greatest number (17,491) occurred in those over 75. There were 26,485 deaths from *bronchitis* (18,997 male and 7,488 female) and 1,098 deaths from *influenza* (553 male and 545 female). Deaths from *cancer of the lung* numbered 22,000 (18,882 male and 3,118 female)—937 more than the 1959 figure. Of the 23 deaths from *acute poliomyelitis* (19 males and 4 females), three were aged 1 to 4 years, two 5 to 14 years, six 15 to 24 years, seven 25 to 44 years, four 45 to 64 years, and the one remaining death was of a man between 65 and 74. Deaths from *measles* in 1960 numbered 31 (but by the end of the first quarter of 1961 there had already been 59 deaths from measles).

Deaths from *accidents* in which motor vehicles were involved numbered 6,643 (4,754 males and 1,889 females). All other accidents accounted for 11,077 deaths (5,510 males and 5,567 females); just over 60% of the women were aged 75 or over. The total of 5,113 *suicides* (3,059 males and 2,054 females) was the lowest number since 1955.—*The Registrar-General's Quarterly Return for England and Wales*, No. 450, 2nd quarter, 1961.

Infective Hepatitis in New Zealand

Infective hepatitis was first made notifiable in New Zealand in 1956. Since then the number of notifications has risen steadily, being 1,973 in 1959 and 3,938 in 1960. Deaths from the disease in 1960 numbered 33, giving a case fatality rate per 1,000 of 8.4. The disease appeared to fall most heavily in those between 5 and 15 years of age, and the evidence suggested that Maoris were more susceptible than Europeans. No district of New Zealand has escaped an outbreak of infective hepatitis during the past four years, and in 1960 Dunedin and Invercargill were particularly heavily hit.—*Report of the Department of Health for the Year Ended March 31, 1961*, Wellington, New Zealand.

Tuberculosis in Foreign Workers in Switzerland

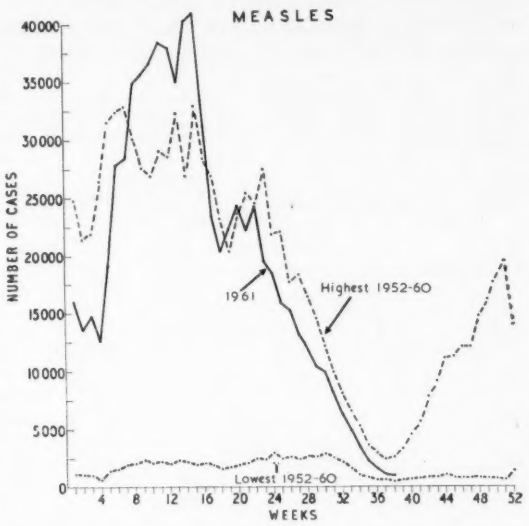
The incidence of tuberculosis among foreign workers in the Swiss canton of Aargau is causing concern. It has been found that 16.8% of 33,000 foreign workers medically examined were suffering from the disease.—*The Times*, October 3.

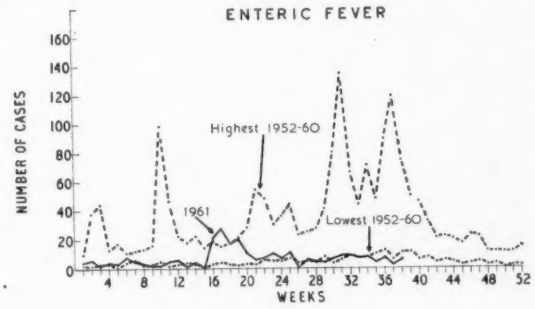
Notifiable Diseases

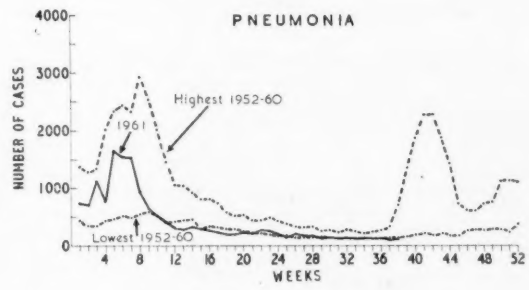
During the week ended September 30 48 cases of food-poisoning were notified in Exeter C.B. and 22 cases in Walsall C.B. Four cases of paratyphoid fever were notified in Keighley M.B.

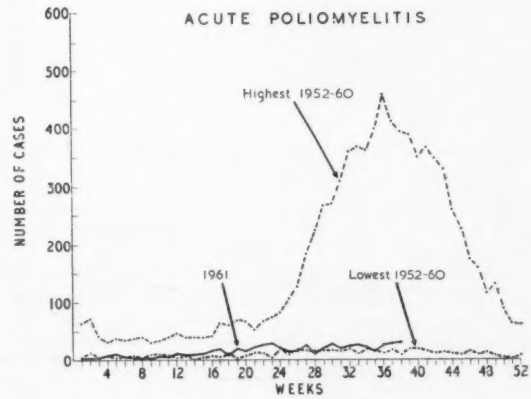
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus - - - - - -, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 23** (No. 38) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	0	0	1	3	0	1	0	1
Dysentery	295	22	172	3	13	434	86	108	9	4
Encephalitis, acute	2	0		0		0	0		0	
Enteric fever:										
Typhoid	4	2	0	0		6	2	0	0	
Paratyphoid	2	0	2(B)	0		9	0	0	0	
Food-poisoning	255	38	37	3		240	28	25	3	
Infective enteritis or diarrhoea under 2 years				13	36				16	33
Measles*	997	39	25	70	36	1,501	48	59	4	2
Meningococcal infection	18	2	6	1		20	0	6	0	
Ophthalmia neonatorum	20	1	3	0		15	0	3	0	
Pneumonia†	99	5	82	1		139	14	86	1	
Poliomyelitis, acute:										
Paralytic	23	2	0	1		3	1	1	1	
Non-paralytic	8	2	0			5	0	1		
Puerperal fever§	189	34	20	0		158	30	12	1	
Scarlet fever	197	14	35	12	11	275	14	43	13	12
Tuberculosis:										
Respiratory	353	41	41	7		357	41	61	13	
Non-respiratory	42	3	6	0		63	6	23	2	
Whooping-cough	287	21	27	6	18	1,132	102	115	14	29

DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		2	0		0	
Encephalitis acute		0			0		1			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	1	0	0	0	5	0	2	1	0
Influenza	2	0	0	0	0	6	0	0	1	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		1	0				0	0		
Pneumonia	405	27	15	15	4	320	29	15	15	3
Poliomyelitis, acute	1	0		0	0	0	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	39	0	5	0	0	50	0	2	1	4
Non-respiratory		0		0	1		0	0	0	1
Whooping-cough	0	0	0	0	0	0	0		0	0
Deaths 0–1 year	274	27	23	6	13	293	25	25	9	6
Deaths (excluding stillbirths)	8,483	656	507	93	120	8,950	713	508	117	142
LIVE BIRTHS	15,817	1374	883	271	359	15,064	1300	1008	306	292
STILLBIRTHS	281	25	20			306	24	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

W.H.O. in Europe

The adoption of a budget of around $1,400,000 for financing the activities of the World Health Organization in Europe, the reappointment for a further five years of Dr. P. VAN DE CALSEYDE as regional director, and the inclusion in the W.H.O. programme of the study of chronic diseases such as rheumatism were the main recommendations made by the W.H.O. Regional Committee for Europe at its recent session in Luxembourg. In his review of the Committee's first decade Dr. van de Calseyde drew attention to the change in priorities since the war. To-day the important problems were accidents, the ageing of the population, the preponderance of cardiovascular diseases and cancer among the causes of death, and the shortage of nurses; these had taken the place of communicable diseases and the reorganization of health services. The campaign against malaria was proceeding satisfactorily, and it was hoped that the disease would be eradicated in Europe in 1962. Dr. M. G. CANDAU, W.H.O.'s director-general, asked European countries to aid the underdeveloped countries of other regions not only with money but by help in training doctors and nurses.

Postage Stamps to Fight Malaria

The member States of the World Health Organization have been invited to arrange a simultaneous issue of postage stamps on April 7 next year to draw attention to the world

programme for the eradication of malaria. Two designs (see above) have been suggested, and though member States will be free to adopt their own it is hoped that they will include the common emblem and the inscription "The World United Against Malaria." The W.H.O. editor comments:

> "It is apparent that the artist has exercised his licence in depicting the insect, but the morphological errors must be accepted in the interests of layout. Perhaps the foreshortening of the proboscis (and palps) may be considered symbolic, but a couchant position would have been more encouraging than the rampant one adopted."

Oral Contraceptives and the F.P.A.

The Family Planning Association's Medical Advisory Council, under the chairmanship of Sir RUSSELL BRAIN, has told the F.P.A.'s National Executive Committee that it considers that "conovid" and, as they are approved, other similar progestogen-oestrogen oral contraceptives may be offered as alternative methods of contraception in F.P.A. clinics provided that (*a*) the pills are administered to suitable cases only under strict medical supervision by medical staff who have been trained in the method; (*b*) the clinic organization is adequate to deal with the administrative problems involved; (*c*) due regard is paid to the relationship between F.P.A. doctors and the rest of the medical profession. The Council considers that closely studied research should be continued in order to evaluate the effects of long-term administration. (See also annotation at p. 1009.)

New Regulations for M.R.C.O.G. and D.Obst.R.C.O.G.

The Royal College of Obstetricians and Gynaecologists has published revised regulations for candidates whose

applications to sit the Membership examination have not been accepted by January 1, 1964, and they will come into force on that date. Briefly, they are as follows. As a matter of immediate policy, in special circumstances, the Council will consider applications from candidates who are not entered on the permanent British *Medical Register*, provided they have fulfilled certain other training requirements. The new regulations provide that no candidate will be allowed to sit the examination until he has been qualified for four years, and fully registered for three. The statutory pre-registration year will be accepted as general medical training. In addition, after registration, candidates will be required to hold recognized posts for six months in general surgery, 12 months in obstetrics and 12 months in gynaecology. Commencing in July, 1964, the examination will include a third paper on "Anatomy, Physiology, Embryology, Endocrinology, Biochemistry, Bacteriology, and Pathology, with Particular Reference to their Application to Obstetrics and Gynaecology." The new regulations for the D.Obst. will apply to all candidates whose applications have not been accepted before January 1, 1963, and will come into force on that date. The most important change is that the six months' training in obstetrics must be held after registration. Fuller details of these changes may be obtained from the Secretary, Royal College of Obstetricians and Gynaecologists, Sussex Place, Regent's Park, London N.W.1.

Specimens by Post

The General Post Office has been greatly concerned recently by a spate of inadequately packed parcels containing pathological specimens, and it would like to point out that though "deleterious liquids or substances" may be sent through the post to a recognized medical laboratory or institute there are post office regulations about it. They must be sent by letter post and on no account by parcel post. The liquid or substance must be enclosed in a "hermetically sealed or otherwise securely closed" receptacle which must be put in a strong wooden or metal case in such a way that it cannot shift about and with sufficient absorbent material about it to prevent any leakage in the event of damage. The packet must be conspicuously marked "Fragile, with Care" and bear the words "Pathological Specimen." Any packet which has not been packed and marked according to these directions or which is sent by parcel post, even if correctly packed, will be at once destroyed. Prosecution may follow. Receptacles supplied by a laboratory or institute should be submitted for inspection to: Postal Services Department, Headquarters Building, General Post Office, St. Martin's-le-Grand, London E.C.1, to find out if they comply with the conditions. Details of special packing and labelling required for overseas postage may also be obtained from this address. In the overseas post pathological specimens are classified as "perishable biological substances" and can be sent only as letter packets between officially recognized laboratories.

Pigeon Post

A Washington practice which runs a suburban health centre in Virginia is training carrier pigeons to help in its work. The birds, carrying specimen phials in a holster on their backs, will be taken by doctors on house calls to fly back specimens for examination at the health centre's clinic. Birds kept at the clinic will be trained to carry specimens to George Washington University Hospital for more detailed examination. (*Daily Telegraph*, September 26.)

Airborne Monkeys

Of a consignment of 395 monkeys carried by air from Nairobi last week over 100 were found to be dead on arrival at the hostel for animals at London Airport. Most of them were intended for use in the manufacture of poliomyelitis vaccine. (See *Journal*, October 10, 1959, p. 704.)

Course for Dental Auxiliaries

The General Dental Council is inviting applications from young women over the age of 17 for a two-year course of training at the School for Dental Auxiliaries at New Cross General Hospital. At the end of their training (simple fillings; extracting deciduous teeth; cleaning, scaling, and polishing) they will be eligible to work in local authority dental services and in the hospital service under the direction of dental surgeons, who will prescribe the treatment to be given.

Practitioners' Guide to Mental Health Act

Sales of *The Practitioners' Guide to the Mental Health Act*, a reprint in leaflet form of an article which appeared in the *Journal* in the last week of 1959, have reached around 16,000. Copies, price 6d., can be obtained from the Publishing Manager, *British Medical Journal*, B.M.A. House, Tavistock Square, London W.C.1.

Mental Health and the Family Doctor

The Minister of Health is sending two booklets to all general practitioners in the National Health Service: *The Part of the Family Doctor in the Mental Health Service*, prepared by the Standing Medical Advisory Committee for the Central Health Services Council and the Minister of Health, and *Notes on the Mental Health Act, 1959, for General Practitioners.*

Disposable Medical Products

An exhibition of "Disposable Medical Products," was held from October 3 to 5 at Grove Park Hospital under the auspices of the Lewisham Division of the British Medical Association. Some 25 firms took part, and the disposable products included blood transfusion equipment, syringes, masks, gloves, sheets, refuse sacks, and bed-pans.

Postgraduate Medical Federation Travelling Fellowships

The British Postgraduate Medical Federation is inviting applications from registered medical or dental practitioners for a limited number of postgraduate travelling fellowships. Details are given on advertisement p. 66.

Coventry and District Voluntary Blood Donors' Association

Nominations are invited for the Coventry Blood Donors' Association Merit Award of £25, which is awarded annually to the nominee who has made outstanding contributions to, or progress in, the science or application of blood transfusion or haematology. Details of the award may be obtained from the Honorary General Secretary, L. G. Griesbach, 6 Delhi Avenue, Foleshill, Coventry, to whom nominations should be sent by December 31.

In Brief

The Food and Drug Administration of the U.S.A. has issued regulations requiring manufacturers of household chemicals to place on any product judged to be highly toxic a label bearing a skull and crossbones, the word "Poison," and the antidote or first-aid treatment.

People in the News

Mr. T. E. Cawthorne is making a three-week working visit to Hungary, Bulgaria, and Yugoslavia under the auspices of the British Council.

COMING EVENTS

University of St. Andrews.—Combined clinical and medical sciences course, restricted to postgraduate students and members of staff. Details from Professor R. B. Hunter, Postgraduate Committee, Medical School, Dundee.

University of Glasgow and R.F.P.S.—Conference, "Diseases of Genetic Aetiology," November 15–17. See advertisement p. 67.

National Association for Mental Health.—Conference, "The Need for Co-operation in Special Services for the Child Delinquent—an Appraisal Following the Ingleby Report," November 15, 10 a.m.–4.30 p.m., Friends' Meeting House, Euston Road, London N.W.1. Admission by ticket only from Conference Secretary, N.A.M.H., 39 Queen Anne Street, London W.1.

Maudsley Lecture, Royal Medico-Psychological Association.—Professor J. Z. Young, F.R.S., "Memory Mechanisms of the Brain," November 15, 2.15 p.m., Royal Society of Medicine, Barnes Hall, 1 Wimpole Street, London W.1. Admission without ticket.

Chest and Heart Association.—Conference, "Stroke Rehabilitation," November 16, 2–4.30 p.m., Arthur Thomson Hall, Medical School, Birmingham 15. Chairman: Dr. E. BULMER. Details and tickets (21s.) from C.H.A., Tavistock House North, Tavistock Square, London W.C.1.

St. Thomas's Hospital Old Students' Dinner.—November 17, 7 p.m., Savoy Hotel, London (entrance, Victoria Embankment). Chairman: Mr. J. F. RYAN. Details and tickets (45s.) from honorary secretary, Mr. W. J. D. BRADFIELD.

National Association for Mental Health.—Residential week-end course for general practitioners, "Psychiatry for the General Practitioner," November 17–19, Waverley Hotel, Southampton Row, London W.C.1. Details from Education Secretary, National Association for Mental Health, 39 Queen Anne Street, London W.1.

Refresher Course for Consultant Ophthalmologists.—February 19–23, 1962, Courage Laboratory, Royal Eye Hospital, St. George's Circus, London S.E.1. Visits included to Maida Vale Hospital for Nervous Diseases and Royal College of Surgeons. Applications to Professor A. SORSBY at the Courage Laboratory by December 1, 1961.

Cambridge University Postgraduate Medical School.—Symposium, "Pain," December 9, 10.30 a.m.; Addenbrooke's Hospital, Cambridge. Details from Secretary, Medical School, Tennis Court Road, Cambridge, before December 2.

NEW ISSUES OF SPECIALIST JOURNALS

The Journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

BRITISH HEART JOURNAL

Factors in the Aetiology of Atrial Septal Defect. Maurice Campbell and P. E. Polani.
Atrial Septal Defect in Three Generations. G. Howitt.
Corrected Transposition of the Great Vessels. W. Beck, V. Schrire, L. Vogelpoel, M. Nellen, and A. Swanepoel.
The Influence of Atrial Size and Elasticity on the Left Atrial Pressure Tracing. Kenneth F. Fairley.
Ventricular Premature Beats in the Diagnosis of Myocardial Infarction. Abdo Bisteni, Gustavo A. Medrano, and Demetrio Sodi-Pallares.
Cardiographic Patterns in Systolic and Diastolic Overload of the Left Ventricle. Ludwik Sedziwy and John Shillingford.
Uses and Fallacies of Intracardiac Electrograms at the Pulmonary Valve. K. K. Datey and M. J. Gandhi.
Clinical and Haemodynamic Observations on Combined Mitral and Aortic Stenosis. M. Honey.
Pulmonary Atresia Developing after a Shunt Operation for Fallot's Tetralogy. J. Fabricius, P. Fritz Hansen, and O. Lindeneg.
The Exercise Electrocardiogram in Patients with Cardiac Pain. H. G. Lloyd-Thomas.
Cardiovascular Involvement in Tropical Eosinophilia. Rustom Jay Vakil.
Atrial Septal Defect with Pulmonary Hypertension. Edwin Besterman.
Cor Triventriculare: Infundibular Stenosis with Subdivision of the Right Ventricle. D. C. Watler and L. Wynter.
Case Report:
Familial Patent Ductus Arteriosus. David Burman.

Volume 23, No. 5. (Bi-monthly; £4 4s. annually.)

GUT

Primary Crohn's Disease of the Colon and Rectum. J. S. Cornes and Mette Stecher.
Difficulties in the Diagnosis and Management of Unsuspected Tuberculous Enteritis and Colitis. E. J. Moran Campbell.
Recurrent Swellings of the Parotid Gland. R. S. Bruce Pearson.
$Co^{58}B_{12}$ Absorption (Hepatic Surface Count) After Gastrectomy, Ileal Resection, and in Coeliac Disorders. D. J. Fone, W. T. Cooke, M. J. Meynell, and E. L. Harris.
Comparative Investigations on the Activity of Leucine Aminopeptidase, Glutamic Oxaloacetic Transaminase, and Alkaline Phosphatase in Serum. B. G. Munck and K. Kjeruff
The Effect of Anticholinergic Drugs on the Electrolyte Content of Gastric Juice. D. W. Piper and Miriam C. Stiel.
Non-esterified Fatty Acids and Lipoprotein Lipase Activity in Patients with Cirrhosis of the Liver. C. Chlouverakis and Peter Harris.
The Effect of Vagotomy and Pyloroplasty on the Maximal Acid Response to Histamine. Alvin M. Gelb, Ivan D. Baronofsky, and Henry D. Janowitz.
The Measurement of Intestinal Sounds in Man and their Relationship to Serum 5-Hydroxytryptamine. B. G. Adams.
The Cardiac Sphincter in the Cat. C. G. Clark and J. R. Vane.
Serum Studies in Man after Administration of Vitamin A Acetate and Vitamin A Alcohol. Oliver Fitzgerald, James J. Fennelly, and Daniel J. Hingerty.
The Problems of Closed Liver Injuries. R. H. B. Mills.
Methods and Techniques:
The Microvilli of the Small Intestinal Surface Epithelium in Coeliac Disease and in Idiopathic Steatorrhoea. Margot Shiner and M. S. Birbeck

Volume 2, No. 3. (Quarterly; £3 annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 16

●HUNTERIAN SOCIETY.—At Talbot Restaurant, 64 London Wall, E.C., 7 for 7.30 p.m., dinner-meeting; 8.30 p.m., Presidential Address by Sir Cecil Wakeley: Chemotherapy of Cancer.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 9.45 a.m., Professor I. Sundberg (Stockholm, Sweden): Treatment of Fistulae in Irradiated Tissues.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. S. Truelove: Treatment of Ulcerative Colitis.

Tuesday, October 17

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Lord Cohen of Birkenhead: "... the elements, So mix'd in him, ...": A study in Human Constitution and Disease.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Bruce Eton: Causes of Onset of Labour.
SOCIETY FOR THE STUDY OF ADDICTION.—At Medical Society of London, 8 p.m., annual general meeting, followed by Kelynack Memorial Lecture by Dr. Gunnar Lundquist (Sweden): Treatment of Alcoholism in Sweden.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. Helen C. Grant: Chronic Meningitis.

Wednesday, October 18

●BIRMINGHAM MEDICAL INSTITUTE: MIDLAND MEDICAL SOCIETY SECTION.—7 for 7.30 p.m., annual dinner; 8.45 p.m., address by Sir David Campbell, F.R.S.: The General Medical Council—Its Powers and Its Work Over a Hundred Years.
HARVEIAN SOCIETY OF LONDON.—8.15 p.m., Dr. J. A. Scott and Miss A. B Read: Social Services in Illness.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. S. Plummer: Actinomycosis and Nocardiosis of the Lung
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. A. H. Harkness: Non-Gonococcal Urethritis.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor Sheila Sherlock: Assessment of Liver Functions.
●ROYAL COLLEGE OF PHYSICIANS OF LONDON.—3 p.m., Harveian Oration by Sir Arthur Thomson: The Consummation of William Harvey.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—3.30 p.m., Professor J. Chassar Moir: The Vesico-vaginal Fistula and its Treatment.
SOCIETY OF MEDICAL OFFICERS OF HEALTH: HOME COUNTIES BRANCH.—At Senior Committee Room, London School of Hygiene and Tropical Medicine, 2.45 p.m., Presidential Address by Dr. A. C. T. Perkins: Is Life a Boon?
WILLESDEN GENERAL HOSPITAL MEDICAL SOCIETY.—At Department of Physical Medicine and Rheumatism, 8.30 p.m., Mr. H. Osmond-Clarke: Pain in the Neck and Arm.

Thursday, October 19

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Presidential Address by Dr. F. G. Spear: Questioning the Answers.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At Beveridge Hall, Senate House, London University, W.C., 5.30 p.m., Professor A. S. Parkes, F.R.S.: External Factors in Mammalian Reproduction.
LEWISHAM GENERAL HOSPITAL.—5.45 p.m., Dr. J. N. Hunt: Assessing Gastric Function.
NORTH WESTERN THORACIC SOCIETY.—At Clinical Sciences Building, York Place, Manchester, 4.30 p.m., Presidential Address by Dr. E. Ratner: 1761 and all that.
●ROYAL SOCIETY OF MEDICINE.—8 p.m., Lloyd Roberts lecture by the Rt. Hon. Enoch Powell, P.C., M.P: Health and Wealth.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5.15 p.m., Dr. J. Hamilton Paterson: postgraduate demonstration in neurology.

Friday, October 20

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—(1) 3.30 p.m., clinical discussion for general practitioners. Miss E. Whetnall: Management of the Deaf Child (2) 4.30 p.m., Annual Address by Mr. J. P. Stewart: Changing Pattern of Acute Mastoiditis.
LEEDS UNIVERSITY: FACULTY OF MEDICINE.—3.15 p.m., Inaugural lecture by Sir John Wolfenden: Crime and Sin.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. Patrick Clarkson: Some Problems in Modern Surgery of the Hand, (2) 4 p.m., Dr. R. H. Girdwood: Investigations of Disease of Small Intestine.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Rabett.—On September 27, 1961, at Central Middlesex Hospital, London N.W., to Jane (formerly Straight) wife of Dr. Robert J. Rabett, a son—Simon James.

DEATHS

Bockett.—On September 25, 1961, at Cork, Ireland, Eric John Cuming Bockett, M.B., B.S., of Farnborough, Hants.
Kemp.—On September 20, 1961, at the Radcliffe Infirmary, Oxford, David Kemp, M.B., Ch.B., D.P.H., of 17 Peppard Road, Caversham, near Reading, Berks, aged 58.
Locke.—On September 16, 1961, at 35 Jackson Road, Newbourne, Woodbridge, Suffolk, Nelson Robert Locke, M.B., Ch.B., aged 35.
Longbottom.—On September 14, 1961, at his home, 2 Grove Park, Knutsford, Cheshire, Donald Longbottom, M.B., Ch.B., D.P.H., aged 48.
Madden.—On September 19, 1961, at St. Bartholomew's Hospital, London E.C., George Madden, M.B., B.Ch., late of 53 Devonia Road, London N.
Nicholl.—On September 19, 1961, at sea, returning from Australia, Joseph Warren McKillop Nicholl, M.D., of Warren House, Lewes, Sussex.
Theron.—On August 3, 1961, at Clanwilliam, Cape Province, South Africa, Agnes Mary Sneddon Theron (formerly Curry), M.B., B.S., D.A., aged 32.
Weller.—On September 17, 1961, at Aldboro' House, Thaxted, Essex, Charles Alexander Weller, M.R.C.S., L.R.C.P.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Canteen Slices

Q.—*Could you please tell me something of the nutritional implications of preparing meat as officially directed by the Army Catering Corps—namely, preheating, slicing, and reheating in order to get the maximum number of thin slices possible from a joint? I gather the same practice obtains in the R.A.F. and in the Navy. One meets it also in many hospitals. Clearly the meat so prepared is less palatable; are there any other adverse effects?*

A.—The procedure mentioned omits the cooling stage, which is presumably introduced after the preheating (cooking). For easy carving the joint of meat is cooked and then allowed to become cold, stiff, and amenable to thin slicing. Later the slices are warmed when wanted for serving the meal. This reheating must cause further losses in addition to those incurred in the first cooking in the more unstable vitamins of the meat, particularly B_1 and C. Since the amounts of these vitamins supplied by the meat are not large the caterer may consider that their loss is unimportant compared with the saving of the skilled labour needed for carving a hot joint and the possibility of making a small helping of meat seem larger than it really is. Caterers who resort to this practice, however, obviously either cannot distinguish between good cooking and bad or must be forced by practical considerations to accept low standards. One may suspect that labour-saving innovations will be placed before palatibility and nutritive value in many other directions. Meals which appear attractive on the menu will prove disappointing in the eating. Failure to stimulate the consumer's appetite may result in greater losses of food through "plate waste" than the savings which are expected to result from the innovations.

Hormones in Treatment of Mongolism

Q.—*Is dehydroepiandrosterone in ten-day courses with ten-day intervals of any value in treating a mongol aged 14 months? If so, how many courses should be given and in what dosage?*

A.—There is as yet no evidence that any hormones are of value in the treatment of sufferers from mongolism. Claims have frequently been made, but they are not supported by properly controlled trials or adequate data. Neither is there any distinct qualitative deficiency in output of male hormones. It is unlikely that injections of dehydroepiandrosterone would have any effect on mental development in a child of 14 months.

Visual Standards for Steel Workers

Q.—*What are the minimum visual standards for workers in the steel industry?*

A.—The law lays down no minimum standards of eyesight for workers in the steel industry. The question is therefore taken to apply in the main to new employees, since it is unusual for regular routine examinations to be performed on all workers in the steel industry. The only exception applies to special groups, such as crane drivers and locomotive drivers. Any standards laid down in a particular works have been arrived at from the experience of the works' medical officer. The following standards are typical.

No workers with monocular vision are engaged, since foreign bodies in the eye are the most common injury in the steel industry and there are difficulties in persuading men to wear protective goggles. In addition, there is the danger of men receiving severe injuries through failing to observe the approach of locomotives and cranes. Crane and locomotive drivers: Distant vision 6/18 in one eye and 6/9 in the other, both correctible to 6/6. Complete correct answers to the stereoptic tests which are found on any of the standard eye-testing machines. In addition, locomotive drivers must have normal colour vision. Other workers: Distant vision of 6/36 correctible to 6/12 with lenses. If the vision is 6/18 or worse they must always wear their spectacles. Variation from the normal vertical and lateral muscular balance would call for examination before engagement so that corrective lenses could be fitted. Near vision is needed to a corrected minimum standard of 6/9 for men engaged in fine work, such as turners, instrument mechanics, and the like.

In a particular works there might be other special groups of workers for whom a standard must be set which is not included in the above list. Such standards could probably be arrived at in consultation with an ophthalmological surgeon.

Alcohol in the Urine

Q.—*In a case of alleged driving under the influence of drink some doubt was thrown on the validity of the alcohol percentage in the urine as a test of sobriety. Factors claimed to influence the alcohol concentration in the urine were the type of drink taken, the quantity of water taken with the spirit, the time the bladder was last emptied, and so on. It appears from the B.M.A. special committee's report[1] that the blood alcohol level is accepted as being a reliable guide, but not the urine alcohol level. I should be grateful for an authoritative opinion on this subject.*

A.—The legal offence is of being "incapable of having proper control of a vehicle," and under existing legislation the percentage of alcohol in the urine can be used only as evidence in support of the clinical findings of other facts before the court. Thus it may serve to exonerate a person from suspicion if there is no alcohol present in the urine, or may test the trustworthiness of a defendant's statement about the amount of drink he has taken. The Tables provided in *The Recognition of Intoxication*[2] give the *minimum* amount of alcohol which must have been taken for different urine concentrations. In compiling these Tables factors such as the type of drink taken and the presence or absence of food in the stomach have been taken into account. In the average case the quantity of drink taken will usually be much greater than the amount calculated from the Tables. Even so, an accused person will often claim to have drunk much less than the amount which urine analysis shows he must have had.

Estimations of the alcohol in urine may also be used as indirect evidence of incapacity to control a vehicle. While it is true that the blood alcohol is a more direct measure of tissue alcohol concentration, urine serves the purpose equally well and has the advantage that samples are easy to collect.[3] There is no statement in the B.M.A. committee's report[1] on the relation of alcohol to road accidents which suggests that urine is less reliable than blood analysis. Drew *et al.*,[3] for example, found a good correlation. The difficulty in using any test which reflects the tissue concentration to indicate the capacity to control a vehicle is the wide variation in the behaviour of different individuals at the same tissue alcohol level. Nevertheless, as the report[1] states, "The Committee cannot conceive of any circumstances in which it could be considered safe for a person to drive a motor vehicle on the public roads with an amount of alcohol in the blood greater than 150 mg./100 ml.," and warns that concentrations over 50 mg./100 ml. impair driving capacity in many persons. The Tables given in the appendix to this report give the equivalent blood and urine figures, and from these it can be seen that these statements will hold true for 200 mg./100 ml. and 70 mg./100 ml. of alcohol in the urine respectively. If the case were properly put in court it is difficult to understand the grounds on which it would be possible to find "not guilty" a person who had been shown to have the higher concentration of alcohol in

the urine. Concentrations much lower than this could be used as confirmatory evidence if the clinical findings were positive.

References

[1] *The Relation of Alcohol to Road Accidents*, 1960. British Medical Association.
[2] *The Recognition of Intoxication*, 2nd edition, 1958. British Medical Association.
[3] Drew, G. C., Colquhoun, W. P., and Long, H. A., *Brit. med. J.*, 1958, 2, 993.

Active Tetanus Immunization in Sensitive Subject

Q.—*A patient of mine aged 14 had an injection of tetanus serum, and six weeks later an injection of tetanus toxoid. She stated that about two days after each of these injections she had some swelling of the face and tenderness of the arm. To test her statement I gave her a subcutaneous injection of 1/16 ml. tetanus toxoid and inspected it 48 hours later, when there was a red flare around the site. Moreover, the girl complained of headache and malaise and some swelling of the face, but no fever. Would you advise me whether I should try to desensitize to the toxoid and/or serum, and what scheme of dosage should be used?*

A.—This patient appears to be somewhat sensitive to tetanus antitoxin and probably also to tetanus toxoid. There was apparently no *severe* general reaction—her headache and malaise, without fever, could feasibly have been coincidental. Nevertheless, she should be actively immunized against tetanus (even at the expense of some temporary discomfort) in order that in the event of a tetanus-prone injury (and provided she carries a record of her immunological history and allergy) she will not be in danger of being given tetanus antitoxin. An attempt should be made to carry out active immunization as soon as possible: after antihistamine drugs have been administered trial doses (0.1 ml.) of tetanus toxoid should be given on each occasion. (A sterile syringe charged with 1:1,000 adrenaline must be available in the unlikely event that it will be required.) If no more than a local reaction occurs (and no unequivocal general reaction) the rest of the dose could be given, say, on the following day. Active immunization should be completed even if it takes time, patience, and one or two nights of moderate discomfort. The end-result—freedom from the necessity of having antitoxin administered—would be worth all the inconvenience. The girl *must* at all times carry on her body or on her clothing a record (in the form of a card, a set of disks, a necklace, or a bracelet) of the fact that in the event of injury she does *not* require to be given tetanus antitoxin.

Subacute Combined Degeneration in the Elderly

Q.—*Is the incidence of onset of subacute combined degeneration of the spinal cord after 75 years known? Has it been observed in anyone over 75 years of age treated with folic acid for non-pernicious anaemia? Has it ever been noted in a person over 75 years whose pernicious anaemia has been treated only with folic acid?*

A.—The precise incidence of subacute combined degeneration of the spinal cord after the age of 75 years is not known. Elderly people often have degenerative changes in the nervous system such as loss of vibration sense, and the use of special investigations to differentiate these from subacute combined degeneration is not always practicable at this age. However, there is no reason to believe that the incidence of unequivocal subacute combined degeneration is any different after the age of 75 from what it is before—i.e., about 7% of all cases of pernicious anaemia.[1] More than 50% of patients with pernicious anaemia develop the disease when over 60 years of age, and the incidence of pernicious anaemia after the age of 75 might well be of the order of 10 per 1,000. Subacute combined degeneration without pernicious anaemia is extremely rare, and the incidence of subacute combined degeneration is therefore unlikely to be higher than 1 per 1,000 of the population over the age of 75.

A summary of cases reported as developing neurological changes after treatment of pernicious anaemia with folic acid is given by Israëls and Wilkinson.[2] Of their own 13 patients who developed subacute combined degeneration during treatment with folic acid one was aged 73. One of the cases reported by Heinle, Dingle, and Weisberger[3] was aged 77. I do not know of any patient over the age of 75 who has developed subacute combined degeneration after being treated with folic acid for *non*-pernicious anaemia. In any event the questioner should realize that subacute combined degeneration never develops unless severe avitaminosis B_{12} is present, whether folic acid is given or not, and pernicious anaemia is the only common cause of avitaminosis B_{12} after age 75.

References

[1] Davidson, S., *Brit. med. J.*, 1957, 1, 241.
[2] Israëls, M. C. G., and Wilkinson, J. F., ibid., 1949, 2, 1072.
[3] Heinle, R. W., Dingle, J. T., and Weisberger, A. S., *J. Lab. clin. Med.*, 1947, 32, 970.

Treatment of Ozena

Q.—*Has any work been done on the treatment of ozena by corticosteroid therapy? Is the disease infectious? In this country (Queensland, Australia) ozena is a rare condition.*

A.—There is evidence that the condition of ozena is becoming much less common in western Europe, and it is interesting to hear that it is seen so rarely also in Australia. There is no evidence that the disease is infectious, although it is known that the crusts do become secondarily infected with saprophytic organisms, notably the cocco-bacillus of Perez. Good results have been reported from the use of various endocrine preparations, especially stilboestrol given locally or systemically, and certain isolated cases appear to have responded to corticosteroid therapy. More recently satisfactory responses have been recorded from the use of cervical sympathetic block and even sympathectomy.

Gas-gangrene Prophylaxis

Q.—*Is it possible to carry out active immunization against gas gangrene?*

A.—It would be possible to prepare vaccines for active immunization against the various gas-gangrene organisms, either separately or in a polyvalent form. But such vaccines are nowadays not required, since gas gangrene can be held in effective check by surgery and antibiotics. Wound excision is the most important prophylactic measure, and should never on any account be unnecessarily delayed. Serum prophylaxis may be combined with surgical treatment: the preparations used are gas-gangrene antitoxin (wel/ser), and, more usually, mixed gas-gangrene antitoxin (gas/ser).

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